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Supreme Court of the United States

October Term, 1980

PREMO PHARMACEUTICAL LABORATORIES, INC., FEDERAL PHARMACAL, INC., SEYMOUR N. BLACKMAN, STEVEN BLACKMAN and JOHN BLACKMAN,

Petitioners,

v.

ELI LILLY AND COMPANY,

Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

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Questions Presented

1. Whether a patent claim reciting a structurally obvious chemical compound can be held valid under 35 U.S.C. §103 solely because the compound possesses an unexpected property not recited in the claim.

2. Whether a patent claim reciting a chemical compound as described in Question 1 can be valid under 35 U.S.C. §§103 and 112 where the unexpected property possessed by the compound and relied on to save the claim from invalidity because of structural obviousness was neither disclosed in the specification and claims of the original application nor even known at the time the application was filed.

3. Whether a patent claim reciting a compound as described in Question 1 can be held valid under 35 U.S.C. §103 where the alleged disclosure of the unexpected property relied on to save the claim from invalidity because of structural obviousness constituted new matter in violation of 35 U.S.C. §132 which was added to the patent application several years after filing thereof.

4. Whether a patent claim reciting a compound as described in Question 1 can be held valid under 35 U.S.C. §§103 and 112 where the alleged disclosure of the unexpected property relied on to save the claim from invalidity because of structural obviousness describes equally well the very prior art compound in view of which the patented compound was held to be structurally obvious.

5. Whether a patent claim reciting a compound as described in Question 1 can be held valid under 35 U.S.C.

§§101, 102(f), 111 and 116 where the unexpected property relied on to save the claim from invalidity because of structural obviousness was discovered by someone other than the named inventors several years after the alleged discovery of the claimed chemical compound by said named inventors.

Parties to the Proceeding Below

The parties to the proceeding in the United States Court of Appeals for the Third Circuit, whose judgment is sought to be reviewed, included as plaintiffs the respondent hereto, Eli Lilly and Company; as defendants, the petitioners herein, Premo Pharmaceutical Laboratories, Inc., Federal Pharmacal, Inc., Seymour N. Blackman, Steven Blackman and John Blackman; and as additional defendants on a counterclaim, Richard D. Wood, C. Harvey Bradley, Jr., Earl B. Herr, Jr., Cornelius W. Pettinga, Eugene L. Step and Arthur R. Whale.

The judgment in the court below which is sought to be reviewed did not involve the aforementioned additional defendants on the counterclaim in any way; and they are, therefore, not named as respondents in this Petition.

TABLE OF CONTENTS

	PAGE
Questions Presented	I
Parties to the Proceeding Below	II
Opinions Below	1
Jurisdiction	2
Statutes and Administrative Rules Involved	2
Statement of the Case	2
A. The History of this Litigation	2
B. Premo's Arguments Against Validity and the Factual Background	5
Reasons for Granting the Petition	13
I. This Case Presents Important Questions of Public Policy Relating to the Monopolization of an Important Drug by Enforcement of a Defective Patent	13
II. This Court Should Resolve the Question of Whether a Structurally Obvious Compound Can Be Patented and Hold that an Unexpected Property Cannot Confer Patentability on a Chemical as a Composition of Matter	16
III. In this Case, a Patent Was Held Valid that Contains a Totally Inadequate Disclosure of the Alleged Invention	22
IV. Other Important Issues of Patent Law Squarely Presented by this Case	25
Conclusion	26

TABLE OF AUTHORITIES

PAGE

Cases:

Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867 (2d Cir. 1971) 15

Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 341 F.Supp. 1303 (E.D.N.Y. 1972), *aff'd on other grounds,* Carter-Wallace, Inc. v. Otte, 474 F.2d 529 (2d Cir. 1972) 17

Carter-Wallace, Inc. v. Otte, 474 F.2d 529 (2d Cir. 1972) 19, 20, 23

Graham v. John Deere Co., 383 U.S. 1 (1966) 15

General Tire & Rubber Co. v. Jefferson Chemical Co., 497 F.2d 1283 (2d Cir. 1974) 20

Monsanto Co. v. Rohm & Haas Co., 312 F.Supp. 778 (E.D. Pa. 1970), *aff'd on other grounds,* 456 F.2d 592 (3d Cir. 1972), *cert. denied,* 407 U.S. 934 (1972) 17, 18, 19, 20

In re Papesch, 315 F.2d 381 (C.C.P.A. 1963) ..... *passim*

Rosenberg v. Groov-Pin Corp., 81 F.2d 46 (2d Cir. 1936) 15

Scott Paper Co. v. Marcalus Mfg. Co., 326 U.S. 249 (1945) 22

Simson Bros v. Blancard & Co., 22 F.2d 498 (2d Cir. 1927) 15

Tinnerman Products, Inc. v. George K. Garrett Co., Inc., 292 F.2d 137 (3d Cir. 1961), *cert. denied,* 368 U.S. 833 (1961) 23

Universal Oil Prod. Co. v. Globe Oil & Ref. Co., 322 U.S. 471 (1944) 22

PAGE

U.S. Constitution:

Art. 1, Sec. 1, Cl. 8 13

Statutes:

28 U.S.C. §1254(1) 2
35 U.S.C. §101 ..... II, 2, 4, 9, 10, 12, 25
35 U.S.C. §102(f) ..... II, 2, 4, 12, 26
35 U.S.C. §103 ..... I, 2, 4, 5, 9, 16, 17, 21
35 U.S.C. §111 ..... II, 2, 4, 12, 25
35 U.S.C. §112 ..... I, 2, 4, 10, 22
35 U.S.C. §116 ..... II, 2, 4, 12, 25
35 U.S.C. §120 ..... 2, 5
35 U.S.C. §132 ..... I, 2, 11, 25
35 U.S.C. §154 ..... 16, 20

Rules of Practice in U.S. Patent Office:

Rule 72(b), 37 C.F.R. §1.72(b) 2, 11, 25

Rules of the Supreme Court of the United States:

Rule 17.1(c) 13

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Petitioners,

v.

ELI LILLY AND COMPANY,

Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

Petitioners pray that a writ of certiorari issue to review the judgment of the United States Court of Appeals for the Third Circuit, entered in the above-entitled case on July 11, 1980.

Opinions Below

The opinion of the United States Court of Appeals for the Third Circuit (Appeal No. 79-1954, filed July 11, 1980) has not been officially reported as of this date. The opinion is set forth in Appendix A hereto. The opinion of the

United States District Court for the District of New Jersey (Civ. Action No. 78-2589, dated July 13, 1979) is also unreported. That opinion is set forth in Appendix B hereto.

Jurisdiction

The judgment of the United States Court of Appeals for the Third Circuit was entered on July 11, 1980. The jurisdiction of this Court is invoked under 28 U.S.C. §1254(1).

Statutes and Administrative Rules Involved

The statutory provisions involved herein are the Patent Act of 1952, 35 U.S.C. §§101, 102(f), 103, 111, 112, 116, 120, 132 and 154. These provisions are set forth in their entirety in Appendix E.

The administrative rule involved herein is Rule 72(b) of the Rules of Practice in the United States Patent and Trademark Office, 37 C.F.R. §1.72(b). This rule is set forth in Appendix E.

Statement of the Case

A. The History of this Litigation

This action was brought on October 27, 1978 in the United States District Court for the District of New Jersey by respondent Eli Lilly and Company (hereinafter referred to as "Lilly") seeking a declaration of validity and enforceability with respect to United States Letters Patent No. 3,507,861 (hereinafter referred to as the " '861 pat-

ent''), dated April 21, 1970, and United States Letters Patent No. 3,655,656, dated April 11, 1972.[1] Lilly also sought preliminary and permanent injunctions against infringement of the aforesaid patents by petitioners Premo Laboratories, Inc., Federal Pharmacal, Inc., Seymour N. Blackman, Steven Blackman and John Blackman (hereinafter collectively referred to as ''Premo'').[2]

Lilly is a giant pharmaceutical corporation manufacturing and selling primarily brand name prescription or ''ethical'' drugs which are usually covered by patents. Premo is a small generic drug corporation which sells generic versions of several brand name ethical drugs, usually at a price much lower than that of the brand name drug.

The '861 patent relates to the antibiotic drug cephalexin. Cephalexin is an orally administrable antibiotic of the family generally known as cephalosporins. The '861 patent is purely a chemical patent, and claims 12 and 16 of the '861 patent recite only the full chemical name of the compound cephalexin in specific or generic form.[3]

An evidentiary hearing on Lilly's preliminary injunction motion with regard to the '861 patent was held at Premo's request on March 16, March 20 and March 23, 1979. The District Court rendered its decision in an opinion

1. The motion was subsequently withdrawn with respect to U.S.L.P. No. 3,655,656.

2. The individual petitioners are officers of Premo.

3. The text of the '861 patent is set forth in full in Appendix F (82a). Claim 12 is a generic claim covering cephalexin and other compounds by chemical nomenclature, while claim 16 is a species claim which by its chemical name recites cephalexin alone.

dated July 13, 1979 (Appendix B, 43a*). In said opinion, the Court held that Lilly had made a sufficient showing to warrant the granting of a preliminary injunction against patent infringement by Premo, and Lilly's motion was therefore granted. The District Court relied on the alleged acquiescence by the pharmaceutical industry in the validity of Lilly's cephalexin patents as supporting the validity of the '861 patent. The Court rejected Premo's arguments that the '861 patent was invalid for obviousness over the prior art under 35 U.S.C. §103 as well as for an inadequate disclosure in the patent specification under 35 U.S.C. §112 and failure to properly join inventors under 35 U.S.C. §§101, 102(f), 111 and 116.[4]

The District Court entered a preliminary injunction order against Premo on July 24, 1979 (Appendix D, 76a).

Premo appealed the District Court's preliminary injunction order to the Third Circuit Court of Appeals which rendered a decision on July 11, 1980[5] affirming the trial court's decision. Like the District Court, the Court of Appeals rejected Premo's arguments that the patent was invalid and found that Lilly was likely to succeed on the merits of its patent infringement claim at trial. The judgment of the Court of Appeals was entered on July 11, 1980 (Appendix C, 74a) and it is that judgment which petitioners seek to have reviewed by this Court.

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* Page numbers in the form "—a" refer to pages in the Appendices.

4. Premo's arguments against the validity of the '861 patent and their factual background are discussed in detail below at pp. 9-12.

5. The opinion of the Court of Appeals is set forth in Appendix A (1a) and the judgment of that Court is set forth in Appendix C.

B. Premo's Arguments Against Validity and the Factual Background

The '861 patent claims priority under 35 U.S.C. §120 based on a parent application which was filed on July 31, 1962.[6]

Both the District Court (67a) and the Court of Appeals (22a-23a) held that the compound cephalexin recited in claims 12 and 16 of the '861 patent was structurally obvious at the time that the parent application was filed in 1962 because its chemical structure results from a minor and well-known structural modification of a previously developed cephalosporin compound, namely, cephaloglycin. Both courts ruled, however, that the '861 patent was not invalid for obviousness under 35 U.S.C. §103 because the compound cephalexin possesses an unexpected pharmacological property which renders it superior to cephaloglycin. Cephalexin is nearly 100-percent absorbed into the blood stream from the digestive tract when administered orally to humans, whereas cephaloglycin is only absorbed to the extent of 20 percent. Both the District Court and the Court of Appeals adopted the viewpoint of the Court of Customs and Patent Appeals set forth initially in *In re Papesch*, 315 F.2d 381 (C.C.P.A. 1963) and held that the patentability of cephalexin should be determined by viewing the compound as a whole, i.e., the chemical structure together with all of its properties, even though the latter are not recited in the claims. Since the structurally obvious compound possesses a property that was allegedly unobvious at the time that the parent application was filed, the lower court held cephalexin unobvious within the meaning of 35 U.S.C. §103.

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6. The parent application, Serial No. 213,588, matured into Patent No. 3,275,626 on September 27, 1966, shortly after the application which matured into the '861 patent was filed.

During the course of the prior proceedings in this case, Premo did not dispute and does not now dispute the fact that the 100-percent "gut" absorbability of cephalexin was an unexpected property at the relevant time in 1962. However, Premo established that neither the parent application, the continuation-in-part application[7] (hereinafter referred to as "c-i-p") which matured into the '861 patent, nor the '861 patent itself discloses this unexpected property. In fact, the parent application did not make any reference at all to the oral absorbability of cephalexin or any of the compounds described therein. The only suggested use of the antibiotic compounds claimed in that application was as "topical sterilants", i.e., preparations applied to the skin, not administered internally.

It was not until 1967, five years after the filing of the parent application and while the c-i-p application was pending that Lilly, not the named inventors, discovered the extremely high absorbability of cephalexin in the human gut, and it was not until September 12, 1968 that an amendment was submitted by Lilly's attorneys adding an Abstract of Disclosure to the c-i-p application which contains the first and only reference to the oral administrability of cephalexin that appears in the '861 patent as issued. The Abstract states that cephalexin is "especially of interest for its use as an antibiotic when administered by the oral route." (83a) The Abstract did *not* disclose that cephalexin was 100-percent absorbed when administered orally or that it in any way was a superior oral antibiotic to cephaloglycin which was an orally administrable antibiotic disclosed in the prior art. In fact, both parties' experts stated that the

7. Application Serial No. 579,222, filed September 14, 1966.

description in the Abstract would apply equally well to cephaloglycin which was being used as an oral antibiotic prior to the advent of cephalexin.

The inventors named in both the parent application, the c-i-p application and the suit patent are Drs. Robert B. Morin and Billy G. Jackson who were research chemists employed by Lilly at the time immediately preceding the filing of the parent application in 1962. The inventors were primarily interested in developing a process for making semi-synthetic cephalosporin antibiotics from penicillins by ring expansion and also in obtaining 3-methyl cephalosporins of a particular chemical structure.[8] Contrary to the statement made by the Third Circuit in its opinion (7a), the inventors were not searching for a new cephalosporin that retained its antibacterial activity upon oral administration. Nor did Dr. Morin and Dr. Jackson look for the chemical substitutions that would "yield a compound that possessed the ultimate characteristic for which industry chemists were searching—that is, effectiveness as an oral antibiotic," as the Court of Appeals asserts (24a). In fact, cephalexin was disclosed in the parent application only as one example of a cephalosporin that could be produced by applying the ring expansion process developed by Drs. Morin and Jackson for producing cephalosporins from penicillins. Many other cephalosporins of similar structure were disclosed as products of this process, and the prop-

8. The basic cephalosporin nucleus which is common to most cephalosporin compounds is known as 7-ACA (4a). 7-ACA has a six-membered ring with a group known as an acetoxymethyl group attached to the ring in what is known as the "3" position. Drs. Morin and Jackson were interested in synthesizing 3-methyl cephalosporins, i.e., cephalosporin compounds where the acetoxymethyl group of the 7-ACA nucleus was replaced by a methyl group.

erties of cephalexin were not distinguished in any way from those of the other new cephalosporins disclosed in the parent application. As indicated previously, the parent application makes no reference to the gut absorbability of cephalexin or any other compound disclosed therein, nor was there any reference to the utility of any of the antibiotics disclosed for oral administration.

In fact, Drs. Morin and Jackson were not aware in 1962 that cephalexin possessed the property of 100-percent absorbability nor even that cephalexin was a particularly good oral antibiotic. This was not known until the discovery in 1967 by another Lilly scientist, Dr. R. S. Griffith, that cephalexin, when administered orally to humans, was superior to prior oral cephalosporins.[9] Although Dr. Griffith was the one who first discovered the property of cephalexin that made the structurally obvious compound patentable according to the lower courts in this case, he was never joined as an inventor in the '861 patent which names only Dr. Morin and Dr. Jackson who were completely unaware of the absorbability characteristics of cephalexin when the parent application to which the '861 patent claims priority was filed in 1962.

The c-i-p application on which the '861 patent issued repeated the disclosure of the ring expansion process which

9. Lilly had discovered by 1965 that cephalexin appeared to have good oral activity in laboratory animals such as mice. The results of pharmacological tests in such laboratory animals, however, are not conclusive of, or necessarily correlated with, the occurrence of such pharmacological activity in man. Only clinical testing on human beings is determinative of the way a drug substance will act on humans, and cephalexin was not even administered to humans until 1967. Premo established that a skilled pharmacologist would not presume from such data that the drug would necessarily have a high absorption rate in human beings.

converted penicillins to cephalosporins and added another method for making 3-methyl cephalosporins.[10] In this application, however, only the antibiotic compounds themselves, as opposed to the process of making them, were claimed. As originally filed on September 14, 1966, the c-i-p application added nothing to the disclosure of the properties of the 3-methyl cephalosporins that was not already present in the parent application. Again, cephalexin was not singled out in any way as having unique properties but was grouped together with all the other cephalosporins produced by the penicillin-cephalosporin conversion process. The only use specified for these compounds, again, was as topical sterilants.

Based on the above facts, Premo had argued before the District Court and the Court of Appeals that the '861 patent was invalid on the following grounds:

1. The '861 patent lists a number of compositions of matter within the meaning of 35 U.S.C. §101,[11] of which one is cephalexin. As a composition of matter, the chemical cephalexin is not patentable because the difference between the chemical structure of that compound and the prior art compounds such as cephaloglycin is such that the compound cephalexin would have been obvious at the time it was discovered to a person having ordinary skill in the art of medicinal chemistry (35 U.S.C. §103). Contrary to the view of the Court of Customs and Patent Appeals in *In re Papesch, supra,* the fact that cephalexin may have possessed a property that was unobvious and unexpected

10. See Footnote 8, *supra.*

11. The texts of the relevant portions of all the statutes and rules cited in this petition appear in Appendix E (78a).

at the time that the compounds were discovered in 1962 did not render the compound patentable at that time. Rather, if the unexpected property of 100-percent absorbability indeed rendered cephalexin a superior oral antibiotic, Lilly could have legitimately obtained a patent on the "new and useful process" (35 U.S.C. §101) of administering cephalexin orally to human beings for the purpose of alleviating certain conditions caused by bacterial infection.[12]

2. 35 U.S.C. §112 requires that the specification of a patent shall contain "a written description of the invention", and the specification must conclude with claims "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." If the invention of claims 12 and 16 of the '861 patent is the compound cephalexin which, in accordance with the *Papesch* doctrine, must be viewed as an antibiotic drug having the unexpected property of being 100-percent absorbable in the human digestive tract, §112 clearly requires that the specification of the patent should have described and the claims should have pointed out and distinctly claimed *that* invention. Since there is no reference in the specification of the patent or in the claims to the 100-percent gut absorbability of cephalexin, which in the *Papesch* theory is an integral part of the invention of this structurally obvious compound, the patent is invalid for failure to comply with the requirements of §112, at least as far as the claims relating to cephalexin are concerned.

3. The only statement in the patent which Lilly claims constitutes a disclosure of the unexpected absorbability

12. Such "medical use" patents are frequently granted by the Patent Office.

trait of cephalexin appears in the Abstract of the Disclosure. As noted previously, that Abstract describes cephalexin as being "especially of interest for its use as an antibiotic when administered by the oral route." That description does not, however, constitute a disclosure of the 100-percent absorbability of cephalexin in any sense. In fact, the description applies equally well to the prior art cephalosporin, cephaloglycin, in comparison with which cephalexin was held to be structurally obvious. The patent thus does not inform the public or the man skilled in the art that cephalexin possesses any unexpected property or any property superior to the prior art cephalosporins.

4. Even if the statement contained in the Abstract could be said to adequately disclose the unexpected property of cephalexin, that Abstract was added to the c-i-p application years after it was filed despite the fact that it constitutes "new matter" in violation of 35 U.S.C. §132. The last sentence in that statutory provision prohibits the introduction of new matter into the disclosure of the invention by any amendment. Thus, the Abstract should not have been permitted by the Patent Office to be added to the c-i-p application in 1968. Furthermore, Lilly is using the Abstract to interpret the claims to cephalexin as including the property of oral administrability. This is directly contrary to Rule 72(b) of the Rules of Practice in the United States Patent and Trademark Office, 37 C.F.R. §1.72(b)[13] which states in relevant part that "[t]he abstract shall not be used for interpreting the scope of the claims." Rule 72 was in effect and included the quoted portion in September, 1968 when the Abstract of the Disclosure was added to the c-i-p application. The error is

13. This Patent Office rule is set forth in Appendix E at 81a.

compounded by the fact that it is the new matter alone which Lilly relied on as a disclosure entitling it to the benefit of the unexpected property to save the claims under *Papesch*.

5. The unexpected property relied on by Lilly to save the claims from invalidity because of structural obviousness was discovered by Dr. Griffith and not by the named inventors, Dr. Morin and Dr. Jackson. Under 35 U.S.C. §§101, 111 and 116, application for a patent must be made by all of the inventors of the alleged invention. In this case, Dr. Griffith must be considered one of the inventors—probably the only inventor of cephalexin as a drug—under Lilly's approach to patentability which dictates that the compound must be considered together with all of its properties in determining whether it indeed constitutes an invention. The patent is invalid under 35 U.S.C. §102(f) because the named inventors "did not [themselves] invent the subject matter sought to be patented." They merely invented the compound cephalexin as a chemical entity which is structurally obvious and thus unpatentable.

Both the District Court and the Court of Appeals rejected the arguments made by Premo and took a totally incorrect view of the law. They held that the unexpected property of 100-percent absorbability could be relied on to support the patentability of the structurally obvious compound cephalexin as a composition of matter; that the specification of the '861 patent sufficiently disclosed and the claims thereof adequately and distinctly claimed the invention, which is cephalexin together with its properties as a drug; that the disclosure of the unexpected property allegedly contained in the Abstract of the invention was

sufficient; that the Abstract of the invention was not new matter and was properly added by amendment in 1968 to the specification; and that Dr. Griffith was not an inventor who had to be named in the application which matured into the '861 patent.

Reasons for Granting the Petition

I. This Case Presents Important Questions of Public Policy Relating to the Monopolization of an Important Drug by Enforcement of a Defective Patent.

Petitioner respectfully submits that the Court should issue a Writ of Certiorari in this case because it presents sharply defined, vitally important questions of federal law which have not been, but should be, settled by this Court.[14] Even more importantly, this case involves issues thoroughly imbued with considerations of public policy, particularly the question of whether the public in this country should be forced to pay exorbitant prices for popular prescription drugs because of monopolies secured on the manufacture, use and sale of those drugs by giant pharmaceutical companies through the acquisition of patents whose subject matter and claims do not meet the constitutional and legislative standards.[15]

The drug at issue in this case, cephalexin, is a very widely used oral antibiotic which has a broad spectrum of antibacterial activity. Until Premo began marketing the generic version of Lilly's cephalexin product in 1978, Lilly

14. Rule 17.1(c) of the Rules of the Supreme Court of the United States.

15. U.S. Const., Art. 1, Sec. 1, Cl. 8; Title 35, United States Code.

was the sole source of cephalexin in the United States by virtue of its patent monopoly on the drug. Premo's generic product was sold to drug wholesalers and distributors for a fraction of the price of Lilly's product, and that substantial saving was usually passed on to the retail level and in turn to patients whose physicians either prescribed cephalexin generically or permitted substitution of a generic product in order to reduce the economic burden of soaring health care costs on their patients. Premo's marketing of generic cephalexin, of course, ceased once the District Court issued its preliminary injunction order (Appendix D) against the alleged infringement of the '861 patent.

Premo vigorously contested this litigation at all stages and asserted a number of meritorious defenses to Lilly's claims of patent infringement. In particular, Premo demonstrated that Lilly's patent on cephalexin is invalid on a number of grounds under the patent statutes—and these grounds are not mere technical points of patent law, but instead, major violations of the spirit and letter of the patent statutes promulgated by Congress pursuant to its constitutional mandate. Premo's arguments were, unfortunately, rejected out of hand by the lower courts which apparently were heavily influenced by secondary considerations such as commercial success and alleged industry acquiescence. Moreover, the lower courts held that public policy considerations dictated that Lilly be awarded the injunction it sought against Premo, totally ignoring the important public policy question of whether one pharmaceutical company should be permitted to have an absolute monopoly for 17 years on an important drug product, reaping enormous profits from a public with no option but to

pay that company's price when the patent in question, which is the heart of the monopoly power acquired by the company, is fatally defective.

It is emphasized that the decision of the Third Circuit which Premo seeks to have reviewed by this Court affirmed a district court decision reached not after a full trial on the merits where Premo would have been accorded an opportunity to put in all its evidence and arguments, but after a hearing on a motion for preliminary injunction. Moreover, that injunction was granted by the district court despite the fact that the federal courts have traditionally frowned on the granting of a preliminary injunction on a patent and have required a very clear showing of validity and infringement[16] before such an injunction could issue.

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16. *See Carter-Wallace, Inc.* v. *Davis-Edwards Pharmacal Corp.*, 443 F.2d 867, 871 (2d Cir. 1971); *Rosenberg* v. *Groov-Pin Corp.*, 81 F.2d 46 (2d Cir. 1936) (Learned Hand, J.); *Simson Bros.* v. *Blancard & Co.*, 22 F.2d 498, 499 (2d Cir. 1927). Judge Hand pointed out in *Rosenberg, supra,* that patent examiners have neither the time nor the assistance to exhaust the prior art and it is common for the best prior art references to be turned up for the first time by a defendant who is sued for infringement of a patent. It is therefore reasonable, stated Judge Hand, not to "tie the hands of the whole art until there is at least the added assurance which comes from such an incentive." 81 F.2d at 47. In *Carter-Wallace, supra,* the Second Circuit noted as an additional basis for the unusually high standard for granting a preliminary injunction on a patent that this Court in *Graham* v. *John Deere Co.*, 383 U.S. 1 (1966), stated that there was a "notorious" difference between the standards applied by the Patent Office and by the courts to the validity of a patent. Therefore, according to the Second Circuit, a preliminary injunction should not be granted unless the validity of the patent is established beyond question.

II. This Court Should Resolve the Question of Whether a Structurally Obvious Compound Can Be Patented and Hold that an Unexpected Property Cannot Confer Patentability on a Chemical as a Composition of Matter.

Aside from public policy considerations relating to the availability of reasonably priced drug products, the issues of patent law in this case have far-reaching implications in the area of the patentability of chemical compounds generally and pharmaceutical compositions in particular. The lower courts in this case held that the '861 patent was valid beyond question even though they recognized that cephalexin is a chemical compound which is closely related in structure to prior art compounds, in particular cephaloglycin, and, indeed, is structurally obvious in light of cephaloglycin. The courts relied on the doctrine expressed by the Court of Customs and Patent Appeals in *In re Papesch, supra,* that in determining the validity of a claim directed toward a chemical compound as a composition of matter, the properties of the compound, even though not mentioned in the claim at all, which recites only the name of the chemical [and thus accords protection under 35 U.S.C. §154 (81a) against anyone making, using or selling the compound *for any purpose whatsoever*] must be taken into consideration as well. If the compound possesses properties which were unexpected and unobvious at the time the patent application was filed, according to the lower courts in this case, the claim to the compound is valid and the patentee secures protection on the compound for *all* uses including uses totally unrelated to the unexpected property which saves the structurally obvious compound from invalidity under 35 U.S.C. §103.

Two well-reasoned district court opinions rejected the *Papesch* decision which upheld the validity of patent claims of a structurally obvious compound because of their properties, pointing out the inconsistency of such an approach with the patent statutes and the potentially devastating ramifications of that doctrine. *Carter-Wallace, Inc.* v. *Davis-Edwards Pharmacal Corp.,* 341 F.Supp. 1303 (E.D.N.Y. 1972), *aff'd on other grounds, Carter-Wallace, Inc.* v. *Otte,* 474 F.2d 529 (2d Cir. 1972); *Monsanto Co.* v. *Rohm & Haas Co.,* 312 F. Supp. 778 (E.D. Pa. 1970), *aff'd on other grounds,* 456 F.2d 592 (3d Cir. 1972), *cert. denied,* 407 U.S. 934 (1972).

In *Carter-Wallace, supra,* Judge Dooling of the District Court for the Eastern District of New York held the patent on the well-known tranquilizer meprobamate (Miltown) invalid for obviousness under 35 U.S.C. §103 despite the fact that the compound possessed unexpected properties as a tranquilizer at the time that the patent was applied for. In his lengthy and learned decision, Judge Dooling set forth his view and that of the cases on which he relied that the patent for a chemical compound, i.e., a composition of matter, must meet a standard of unobviousness against the *chemical* prior art; the fact that the compound may have a property that is unobvious to one skilled in different disciplines such as pharmacology or medicine cannot confer patentability on the compound unless that property is set forth in the claim and in the specification. Once the composition of matter, in the present case cephalexin, is conceived and made, the inventive act is complete as to the chemical compound. If the compound that has been created is obvious in view of the prior compounds, the later dis-

covery of a special property possessed by the compound and not recited in the claims and specification cannot confer unobviousness on it as a composition of matter.[17]

Judge Dooling's arguments are particularly appropriate to the situation which occurred in this case. Cephalexin is disclosed in the parent application and in the c-i-p application as filed only as a possible product of the chemical ring expansion processes described therein. Cephalexin's 100-percent absorbability was not known or recognized at the time of the filing of said applications, and, as a result, it could not have been and was not disclosed in said applications. Yet, the inventive act had to have been complete in 1962, well before the discovery of the unexpected property; otherwise, Lilly should not have had the benefit of the filing date of the parent application as far as the application of prior art is concerned.[18]

In *Monsanto* v. *Rohm & Haas, supra,* the Court took the view that structural obviousness in and of itself precludes a patent on a new compound as a composition of matter. The Court suggested that if what makes a structurally obvious chemical substance patentable is a new or unobvious property or a new use, the discoverer should have patent protection precisely limited to his discovery, i.e., to the exploitation of the new properties or the new uses. The Court stated:

> "To say that a person who has discovered a new use for a structurally obvious compound, which compound would not have been entitled to any patent protection absent the new use, should receive a patent on the

17. See 341 F.Supp. at 1337-38.

18. See Footnote 21, *infra.*

> compound itself is to extend the patent monopoly far beyond the reason for its existence. We think that the purposes of the patent law will be adequately served if patents on compounds which are structurally obvious from the prior art are limited to method patents directed to the new and useful characteristic or property which is the essence of the discovery or invention." 312 F. Supp. at 791.

Applying this reasoning to the present case, the use of cephalexin as a drug for oral administration having the property of 100-percent gut absorbability might well be patentable, but the structurally obvious chemical itself is not patentable. Since claims 12 and 16 are composition of matter claims, not method claims, and describe only the bare chemical cephalexin, the *Monsanto* case analysis is directly applicable. Certainly if a company other than Lilly had discovered the chemical structure of the compound cephalexin and Lilly's scientists subsequently had only discovered the unexpected property of the compound when used for a particular purpose, Lilly would not be claiming that the discoverer of the compound itself was the inventor of the drug possessing the unexpected property.

On the appeal of Judge Dooling's decision discussed above,[19] the Second Circuit found it unnecessary to decide whether Judge Dooling was right in holding that a claim for a structurally obvious composition of matter could not be saved because the compound had an unexpected property. The reason for this was that the unexpected property had not been disclosed, so Carter-Wallace was not entitled to the benefit of that property to save its patent from obviousness even under the *Papesch* doctrine. It may be that,

19. *Carter-Wallace, Inc.* v. *Otte*, 474 F.2d 529 (2d Cir. 1972).

for the same reason, this Court would not have to pass on this question either. However, it is thought that the law relating to chemical patents, particularly in the pharmaceutical field, is in great need of clarification, and the Court is respectfully urged to address the question of whether a structurally obvious compound is patentable as a composition of matter under these circumstances.[20]

It is believed that Judge Dooling's analysis is clearly the correct one and that the patent laws should not be twisted in a way such as to permit a party to obtain a patent on a structurally obvious chemical merely because it has an unpredicted property. A use patent claim limited to the exploitation of unexpected properties, in this case a claim to the use of cephalexin as an orally administrable antibiotic, might be patentable. But Lilly's claims in suit are composition of matter claims unlimited in any way other than to define the chemical cephalexin by its chemical name. If the claims in question are valid under 35 U.S.C. §154, no one but Lilly can make, use or sell cephalexin for *any* purpose, even a non-medical use where the unexpected property has no value whatsoever.

A further incongruous result which is led to by the approach to the patentability of chemical compounds taken by the lower courts herein is well illustrated by the facts in this case. Lilly's parent application was filed in 1962 when the compound cephalexin was conceived by Drs.

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20. Two years after the decision in *Carter-Wallace, Inc.* v. *Otte, supra,* the Second Circuit had another opportunity to rule on this question and again declined. *General Tire & Rubber Co.* v. *Jefferson Chemical Co.,* 497 F.2d 1283 (2d Cir. 1974). The Court does refer to the *Monsanto* case and Judge Dooling's decision as "even more forcefully" arguing the view that where a composition of matter is chemically obvious, only a use patent should be available.

Morin and Jackson. At that time, neither the named inventors nor anyone else was aware of the unexpected pharmacological property possessed by cephalexin. Therefore, if a patent had issued to Lilly containing claims to the compound cephalexin in 1964, for example, and Lilly had subsequently sued for infringement of that patent, the claim to cephalexin would have been held invalid even by the very District Court and Court of Appeals who ruled in this case because they would have held the chemical to be structurally obvious and there would have been no evidence of any unobvious property which could have saved the patent claim from invalidity under 35 U.S.C. §103. But, according to the *Papesch* doctrine adopted by the lower courts herein, when Lilly discovered that cephalexin was 100-percent absorbable in the human gut in 1967, that discovery retroactively conferred patentability on the compound, and not as of 1967, but as of the filing date of Lilly's parent application in 1962.[21] Thus, a compound which for years was unpatentable and patent claims which for years were invalid, were miraculously converted to validity by the discovery of a property in 1967, which discovery was made by a person not even named in the patent as an inventor, though it is clear that without his discovery, there could have been no patentable invention even under the *Papesch* doctrine.

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21. Because Lilly was able to get the benefit of its 1962 filing date for the '861 patent even though the property which, according to the lower courts in this case, saved the patent claims from invalidity was not discovered until 1967, Premo was unable to use any prior art references which were dated after the 1962 filing date of the parent application. Thus, although the claims to cephalexin would have been held invalid even by the lower courts herein prior to the discovery of the unexpected property in 1967, no attack could be made on the validity of the patent on the ground of obviousness based on prior art dated between 1962 and 1967.

III. In this Case, a Patent Was Held Valid that Contains a Totally Inadequate Disclosure of the Alleged Invention.

This Court has held on several occasions that the whole purpose for the existence of patents, which, *prima facie,* are contrary to the general rule of free and open competition in our society, is to encourage the disclosure of inventions to the public who may practice those inventions once the patent has expired. Furthermore, this Court has called the disclosure of invention the *quid pro quo* which the inventor must give in return for being awarded a patent monopoly.[22] Lilly has failed to comply with the important disclosure requirements of the patent laws and thus the '861 patent is invalid and should have been held invalid by the lower courts.

Even if, *arguendo,* the *Papesch* doctrine is accepted and cephalexin could be saved from invalidity as a structurally obvious compound by its unexpected pharmacological property, it is clear that the property relied on for patentability must be specifically disclosed in the specification of the patent. 35 U.S.C. §112 (79a), discussed previously[23] requires that the specification contain a clear, concise and exact description of the invention and that the claims of the patent particularly point out and distinctly claim the subject matter of the invention. According to the District Court and Court of Appeals in this case, Lilly's invention embodied in the '861 patent is the compound cephalexin

22. *Scott Paper Co.* v. *Marcalus Mfg. Co.,* 326 U.S. 249, 254-56 (1945); *Universal Oil Prod. Co.* v. *Globe Oil & Ref. Co.,* 322 U.S. 471, 484 (1944).

23. P. 10, *supra.*

together with its unexpected property of 100-percent absorbability from the human digestive tract—yet that property, which is crucial to the patentability of cephalexin, is nowhere disclosed in the patent.

In *Carter-Wallace, Inc.* v. *Otte, supra,* the Second Circuit invalidated the patent on meprobamate because the allegedly unexpected properties of the drug as a tranquilizer were not disclosed in the patent. The Court held that:

> "[T]he novel, unexpected, or superior unobvious property must be disclosed in the patent application or at least in supporting documents in order to be relied upon as a basis for patentability."

474 F.2d at 540 (footnote omitted). Carter-Wallace's answer to the foregoing was an argument similar to Lilly's argument in the present case that the tranquilizing property was in fact disclosed. The Court disagreed and was prompted on the Petition for Re-Hearing to emphasize the high standard of disclosure required:

> "We reiterate that a high standard of disclosure is required before a novel property of an otherwise obvious chemical compound can be relied upon to establish patentability."

Id. at 548.

Similarly, the Third Circuit in *Tinnerman Products, Inc.* v. *George K. Garrett Co., Inc.,* 292 F.2d 137 (3d Cir. 1961), *cert. denied,* 368 U.S. 833 (1961) rejected an argument that an undisclosed property could be relied upon for patentability and stated the following:

> "The difficulty with this basis for patentability (even assuming it to be an advantage over the prior

> art) is that nowhere in the specifications, claims, or file wrapper of the patent, is this advantage either disclosed or claimed. The applicable law is clear that where the particular feature relied upon is nowhere mentioned as an advantage, it cannot form the basis of patentability."

Id. at 140.

These cases point out that if the *Papesch* doctrine is to be used, it should be at least applied only where the allegedly unexpected property was clearly disclosed in the patent. In the present case, Lilly did not disclose the unexpected high oral absorbability of cephalexin in the parent application or in the c-i-p application (and was not even aware of that property of the compound until after the c-i-p application was filed). It was only in 1968 that Lilly added its Abstract of the Disclosure to the patent which, while it refers to use of cephalexin by oral administration, still is wholly inadequate to apprise the public of the unexpected property, i.e., 100-percent gut absorbability of cephalexin in human beings.[24] In fact, the disclosure in the Abstract of the oral usefulness of cephalexin applies equally well to cephaloglycin, and there is no reason for anyone reading the disclosure to even use cephalexin as an oral antibiotic in place of cephaloglycin.

Lilly simply failed to disclose at any time the unexpected property of cephalexin which turned out to be the only feature that rendered the compound patentable under

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24. It was pointed out previously that the disclosures in the supporting affidavits submitted by Lilly which related only to animal testing data certainly did not constitute a disclosure of the 100-percent absorbability property in humans. *See* Footnote 9, *supra*.

the *Papesch* doctrine. Therefore, even if *Papesch* is adopted, the '861 patent should have been held invalid by the lower courts.

IV. Other Important Issues of Patent Law Squarely Presented by this Case.

The Third Circuit accepted Lilly's argument that the disclosure in the Abstract of the oral usefulness of cephalexin was a sufficient disclosure of the unexpected absorbability property. But even if that disclosure were adequate, it was not properly added to the specification of the '861 patent because it constituted new matter, the addition of which to a patent specification violates 35 U.S.C. §132 (80a). Moreover, Rule 72(b) of the Rules of Practice in the United States Patent and Trademark Office, 35 C.F.R. §1.72(b) (81a) specifically states that an Abstract is not to be used in interpreting the scope of the claims of the patent. Lilly wishes to do exactly that which is prohibited by the Patent Office rule, namely, to interpret the claims which recite only the chemical name of cephalexin as incorporating the alleged disclosure of the unexpected property contained in the Abstract.

Another important point is raised by Premo's argument that if the unexpected property relied on for patentability was discovered by Dr. Griffith in 1967, Dr. Griffith should have been joined as an inventor pursuant to 35 U.S.C. §§101, 111 and 116 (78a, 79a, 79a). The '861 patent as issued names only Dr. Morin and Dr. Jackson as the inventors, but they clearly did not discover the property of cephalexin which, according to the lower courts herein, confers patentability on the structurally obvious compound.

Therefore, the patent should be invalid under 35 U.S.C. §102(f) (78a) because the named inventors merely discovered the unpatentable cephalexin and not the true "invention" embodied in the patent which, under the theory of *Papesch,* is cephalexin together with its unexpected pharmacological property.

Conclusion

For the above reasons, it is respectfully submitted that a Writ of Certiorari should be issued to review the judgment of the United States Court of Appeals for the Third Circuit.

Respectfully submitted,

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Appendices

APPENDIX A

Opinion of the United States Court of Appeals for the Third Circuit July 11, 1980

(not yet officially reported)

UNITED STATES COURT OF APPEALS

FOR THE THIRD CIRCUIT

No. 79-1954

ELI LILLY AND COMPANY,

v.

PREMO PHARMACEUTICAL LABORATORIES, INC.,
Federal Pharmacal, Inc.,
Seymour N. Blackman, Steven Blackman,
John Blackman,

Appellants,

v.

Richard D. Wood, C. Harvey Bradley, Jr.,
Earl B. Herr, Jr., Cornelius W. Pettinga,
Eugene L. Step and Arthur R. Whale,

Additional defendants on the Counterclaim.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
(C.A. No. 78-2589)

Argued February 14, 1980

Before: ADAMS, VAN DUSEN and GARTH, *Circuit Judges*

(Filed July 11, 1980)

OPINION OF THE COURT

ADAMS, *Circuit Judge.*

On this appeal from an order granting preliminary injunctive relief in a patent case, we are presented inter alia with the provocative question whether, in determining that a new chemical compound was "nonobvious" in view of prior art, all of the properties of the drug may be considered, or whether the structural similarity between the new compound and the prior art constitutes a per se bar to patentability. Appellant also raises several other issues regarding the validity of the patent at issue here, and urges that the district court abused its discretion in granting the preliminary injunction. Inasmuch as we conclude that the "structural obviousness" of a new compound is not a bar to patentability, that the district court did not err in applying the applicable law, and that the court did not abuse its discretion in granting injunctive relief, we affirm.

FACTUAL BACKGROUND

A. The Parties and Procedural Posture of the Case

Eli Lilly and Company is engaged in the business of research, development, manufacture, and sale of ethical pharmaceutical products. It invests approximately ten percent of its net sales revenue in research and development, and in 1978 such expenditures exceeded $140 million. The company has acquired patents on many of its products which, it claims, are "a cornerstone of the research efforts that in turn have led to the development of new products."[1]

Premo Pharmaceutical Laboratories, Inc. is engaged primarily in the manufacture and sale of generic pharma-

1. Brief for Appellee at 4.

ceutical products that are duplicative of drugs developed and manufactured by research-oriented companies. Because Premo has only a small research and development budget, it is generally able to sell its products at prices lower than those offered by competitors that engage in more extensive research and development.

Eli Lilly owns patents for cephalexin, an oral antibiotic that is commonly used as a substitute for penicillin.[2] Upon learning that Premo had acquired a large quantity of cephalexin from Italy and was planning to sell the drug in the United States, Eli Lilly brought this action for declaratory judgment, preliminary and permanent injunctive relief, and damages. Following several months of discovery, Eli Lilly applied for a preliminary injunction by which it sought to enjoin Premo from selling cephalexin. The primary question presented in the district court was whether the patent is valid.[3]

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2. The patent for cephalexin monohydrate, entitled "Certain 3-Methyl-Cephalosparin Compounds," is U.S. Patent No. 3,507,861 (hereinafter '861 patent). Eli Lilly also owns the patent for an invention entitled "Crystalline Cephalexin Monohydrate," U.S. Patent No. 3,655,656 (hereinafter '656 patent). The latter, commonly known as "dense form cephalexin," is a type of cephalexin monohydrate that is especially suitable for oral administration. This appeal involves only the '861 patent.

The validity of both the '656 and '861 patents was the subject of an earlier suit for declaratory relief brought against Eli Lilly by Zenith Laboratories, Inc. The case was settled after the district court granted Eli Lilly's application for a preliminary injunction that enjoined Zenith from selling dense form cephalexin in violation of the '656 patent. Much of part I of today's opinion is drawn from Judge Meanor's extensive and detailed description of the structure and development of cephalexin and its precursors that is set forth in the opinion in the *Zenith* case. Zenith Laboratories, Inc. v. Eli Lilly and Co., 460 F. Supp. 812 (D.N.J. 1978).

3. Premo conceded that if the '861 patent is valid, Premo's product infringes it. Also, Premo made no claim that cephalexin is not a "new and useful" product within the meaning of 35 U.S.C. § 101 (1976), or that cephalexin lacked "novelty" as defined by 35 U.S.C. § 102 (Supp. II 1978).

After conducting an extensive hearing, the trial court entered an order on July 24, 1979 preliminarily enjoining Premo from infringing the patent by "the manufacture, use, sale, offering for sale, or promoting or inducing the sale in the United States, its territories or possessions, of cephalexin."[4] In its opinion, the court held that (1) the creation of cephalexin was not merely an obvious extension of the prior art, because the drug yielded the unexpected property of being almost 100% absorbable into the bloodstream; (2) Eli Lilly adequately disclosed this characteristic in its patent application; (3) Eli Lilly therefore established a sufficiently high probability that it would succeed on the merits of its claim to warrant the issuance of a preliminary injunction; and (4) Eli Lilly would be irreparably harmed if Premo were permitted, even temporarily, to sell cephalexin.[5] Premo filed a timely appeal.[6]

B. The Development of Cephalexin

Cephalexin monohydrate is a member of the cephalosporin family of antibiotic drugs. Cephalosporins are derived from the fungus *Cephalosporium acremonium* and contain a nuclear ring structure not otherwise found in nature. The common structural characteristic of the cephalexin family is formed by a six-membered ring of 7-aminocephalosporanic acid (7-ACA). The various cephalosporins differ from one another in the number and type

4. Preliminary Injunction Order, July 24, 1979, App. 66.

5. Eli Lilly & Co. v. Premo Pharmaceutical Laboratories, Inc., Civ. No. 78-2589, slip op. at 12-26 (D.N.J. filed July 13, 1979). Premo conceded that Eli Lilly owned the patent, and that, if the patent is valid, Premo had infringed it.

6. Appellate jurisdiction is conferred by 28 U.S.C. § 1292(a)(1) (1976).

of side chains attached to the seven-position of the nucleus and the type of substituent attached to the three-position of the nucleus.[7] While all cephalosporins have approximately the same range of antibiotic activity and toxicity, the structural variations result in different pharmacological properties. That is, each cephalosporin reacts differently with the human body.

As a group, cephalosporins are uniquely effective antibiotics. Bacteria are commonly classified in two basic groups: those that take the so-called Gram stain are termed Gram-positive; those that reject the stain are termed Gram-negative. Penicillin is active only against Gram-positive bacteria. In contrast, cephalosporins are effective against both Gram-positive and Gram-negative bacterial strains. Cephalosporins also have low toxicity and allergenicity, and therefore produce relatively few adverse side effects and allergic reactions. As a consequence, cephalosporins are frequently used to treat individuals who are allergic to penicillin.

The parent compound of the cephalosporin family, Cephalosporin-C, was first isolated in the 1950's by two British scientists, Professor E. P. Abraham and Dr. G. G. F. Newton.[8] In the early 1960's, scientists discovered a method of isolating the 7-ACA nucleus and of appending various side chains and substituents in order to create a variety of cephalosporins more potent than Cephalosporin-C. The method of isolation was expensive, however, which made commercial production of cephalosporins infeasible at that time. Shortly thereafter, the National

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7. Diagrams of the cephalosporin nucleus, as well as cephaloglycin and cephalexin are reproduced in the appendix, *infra*.

8. *See* Abraham & Newton, *New Penicillins, cephalosporins C and penicillinase,* Endeavor, April 1961, at 92.

Research Development Corporation, a Crown agency of Great Britain founded to assist the commercialization of British inventions, began promoting cephalosporin research. The Corporation entered into agreements with a number of pharmaceutical companies under which the companies promised to participate in cephalosporin research and to make their findings available to the Corporation in exchange for access to the results of prior research and other assistance. Eli Lilly was a party to this accord.

Eli Lilly was the first company to develop a cost-efficient method of producing a 7-ACA nucleus, and by early 1962 its first cephalosporin antibiotic was ready for clinical testing. In 1964, it began marketing a form of cephalosporin, cephalothin, under the trademark "Keflin," and, in 1968, introduced cephaloridine under the brand name "Loridine." These drugs were effective antibiotics only when administered intravenously, however, because they were not sufficiently absorbed into the blood stream from the digestive tract to make oral administration feasible. Consequently, Eli Lilly began experimenting with the side chain attached to the 7-ACA cephalosporin nucleus in order to construct an orally effective form of cephalosporin. It achieved this goal by substituting a phenylglycine side chain at the 7-position. The company's research consultant, Edwin H. Flynn, who was extensively involved in the research, has stated that this result was surprising because identical experimentation with the penicillin nucleus had made that drug active against Gram-negative bacteria—a trait that cephalosporins already possessed.[9] The first orally administerable cephalosporin was called

9. Affidavit of Edwin H. Flynn, Nov. 27, 1978, at 8-9. App. 105, 112-13.

cephaloglycin and was marketed in 1970 by Eli Lilly under the trademark "Kafocin."

Cephaloglycin was found to be eighteen to twenty-two percent absorbed into the bloodstream, which is a sufficient percentage to be a satisfactory oral antibiotic. More than half of the cephaloglycin absorbed, however, underwent a chemical conversion that substantially diminished one of its most useful properties—effectiveness against Gram-negative bacteria.

In the course of the search for an orally administerable cephalosporin that also retained its activity against Gram-negative bacteria, two researchers at Eli Lilly, Dr. Robert E. Morin and Dr. Billy G. Jackson, discovered a novel chemical reaction by which various penicillins could be converted into a type of cephalosporin compound that contains a methyl group at the 3-position in place of the acetoxymethyl group that naturally exists at that position of the cephalosporin nucleus. Although the 3-methyl cephalosporin, unlike cephaloglycin, underwent no chemical changes upon absorption, and therefore remained completely active against Gram-negative bacteria, the scientists found that the drug displayed a markedly lower level of activity than corresponding cephalosporins that contain the natural acetoxymethyl group. As a result, Eli Lilly directed its research away from 3-methyl cephalosporin.

Following a series of unsuccessful experiments with other forms of cephalosporin, Drs. Morin and Jackson urged their colleagues to test once again 3-methyl cephalosporin. In 1965, the researchers subjected cephaloglycin to hydrogenolysis to form the 3-methyl cephalosporin that later came to be known as cephalexin. Cephalexin retained the 3-methyl cephalosporin characteristics of being completely active against Gram-negative bacteria and exhibit-

ing a reduced level of activity. However, cephalexin yielded the unexpected property of being absorbed virtually one hundred percent into the bloodstream and completely excreted in the urine without chemical alteration. The one hundred percent absorption rate more than offset the reduction in the level of activity.[10] As a result, cephalexin is a highly effective oral antibiotic.[11] Eli Lilly obtained a patent for cephalexin on April 21, 1970.[12] It is the question of the validity of this patent that is before us today.

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10. The so-called Morin-Jackson process, entitled "Penicillin Conversion Via Sulfoxide," is protected by U. S. Patent No. 3,275,626.

11. In its original form, cephalexin, although effective when administered orally, was not well-suited for oral consumption. The cephalexin molecule was originally produced at room temperature as a dihydrate. Because the dihydrate crystals were so bulky and fluffy, a full dose could not be put into a single capsule of acceptable size. On drying, the dihydrate crystals are converted into monohydrate crystals. The cephalexin monohydrate thus formed was also bulky, however, and the crystals tended to pick up a static charge, which made handling and encapsulation impracticable on a commercial basis.

Accordingly, Eli Lilly began searching for an alternative method of producing cephalexin. Dr. Earle Van Heyningen, an Eli Lilly scientist, discovered a process of crystallizing cephalexin monohydrate at temperatures greater than 60 degrees centigrade such that the crystals obtained were relatively large, nonhygroscopic, dense, and nonelectro-statically excitable. These crystals could be encapsulized relatively easily, and were small enough so that a single dose would fit into a capsule of acceptable size. The patent for this dense form cephalexin was issued on April 11, 1972. U.S. Patent No. 3,655,656. *See* note 2 *supra*. Eli Lilly markets most of its cephalexin in this form under the trademark Keflex.

The patent for dense form cephalexin (the '656 patent) is premised on the validity of the patent for regular cephalexin (the '861 patent) which is at issue in this case.

12. U.S. Patent No. 3,507,861.

C. Eli Lilly's Production and Marketing of Cephalexin

From 1958 to 1977, Eli Lilly invested approximately $10 million in the research and development of cephalexin. The research included the chemical synthesis experiments described above, "laboratory evaluations *in vitro* and *in vivo*, development of analytical methods, development of processes for the production and purification of cephalexin monohydrate as a chemical product, [and] animal and human pharmacology and metabolism studies."[13] From 1968 to 1977, Eli Lilly spent more than $1.8 million on clinical testing of cephalexin on human beings. A substantial portion of this sum was used to fund studies required by the United States Food and Drug Administration (FDA). Eli Lilly spent more than half of the $1.8 million in post-marketing studies that were designed to adduce additional information about the effectiveness and potential dangers of cephalexin.[14]

Eli Lilly has been quite successful in marketing cephalexin. Cephalexin has become the most widely prescribed oral cephalosporin in the United States, and is the most common substitute for oral penicillin administered to penicillin-allergic patients. Moreover, because of its greater absorption rate, cephalexin generally competes well against ampicillin, penicillin, and other cephalosporins.

D. The Response of the Pharmaceutical Industry to Eli Lilly's Patent on Cephalexin

In general, the other members of the domestic pharmaceutical industry appear to have been interested in sell-

13. Zenith Laboratories, Inc. v. Eli Lilly & Co., 460 F. Supp. 812, 816-17 (D.N.J. 1978).

14. In addition, during the first two years of distribution, Eli Lilly expended approximately $12.3 million on a variety of activities designed to promote the prescribing by physicians of cephalexin.

ing cephalexin, but to have refrained from challenging Eli Lilly's patents. From 1970, when the first patent on cephalexin was issued, until 1977, Eli Lilly was the sole seller of cephalexin in the United States. During that period, two small domestic drug companies sought to obtain licenses to manufacture cephalexin, but Eli Lilly denied their requests. Four multinational pharmaceutical companies that manufacture cephalexin abroad or have the capacity to produce it here thus far have respected Eli Lilly's patent. None of these companies has a license or other agreement with Eli Lilly that would be jeopardized by an attempt to enter the United States cephalexin market.[15]

Zenith Laboratories, Inc., a domestic producer of generic drugs, began marketing cephalexin in this country in 1977. Zenith produced very little of the drug itself and obtained most of its supply from an Italian manufacturer. Following the issuance of a preliminary injunction against such sales, however, Zenith voluntarily withdrew from the market.[16]

In August or September 1978, Premo advised Eli Lilly that it had obtained large quantities of cephalexin from foreign manufacturers, had put cephalexin into dosage-sized capsules, and was planning to sell the drug in the United States. Premo also stated that it believed Eli Lilly's patent on cephalexin was invalid and therefore unenforceable. In response to this information, Eli Lilly brought the present action to declare the patent valid and to enjoin Premo, preliminarily and then permanently, from selling cephalexin in the United States.

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15. Zenith Laboratories, Inc. v. Eli Lilly & Co., 460 F. Supp. 812, 818 (D.N.J. 1978).

16. The injunction covered only the patent on dense form cephalexin (the '656 patent). *See* notes 2 & 11 *supra*.

II. ISSUES PRESENTED ON APPEAL

On this appeal, Premo raises a number of related contentions. First, it argues that the district court erred in holding that, although structurally obvious in light of prior art, cephalexin was nevertheless patentable because it yielded the unanticipated and nonobvious characteristic of one hundred percent absorbability into the bloodstream. Second, it urges that, even if the district court did not so err, Eli Lilly's patent is invalid because the company did not adequately disclose the absorbability trait in either the patent or in the patent application. Third, it claims the patent is invalid because Eli Lilly disclosed the trait in an amendment to the original Abstract of Disclosure in violation of the statutory prohibition against introducing new matter by amendment. Fourth, it maintains that the patent is invalid because the unexpected property in fact was discovered by someone other than the persons listed in the patent application as the inventors. Fifth, it disputes the district court's conclusion that other domestic drug manufacturers acquiesced in Eli Lilly's patent on cephalexin. Sixth, it contends that the district court abused its discretion in granting the preliminary injunction. We shall address these claims seriatim.

III. DISCUSSION

A. Validity

Eli Lilly's patent on cephalexin was valid, according to the district court, for two reasons: (1) Eli Lilly had complied with all statutory requirements. (2) The pharmaceutical industry's acquiescence in the patent represents

sufficient circumstantial proof that the patent is valid. Inasmuch as we conclude that the patent is valid because Eli Lilly fulfilled all statutory requirements, we have no occasion to address the latter basis for the district court's decision.

1. Structural Obviousness and the Unanticipated Trait

The Patent Act of 1952[17] sets forth three general requirements for patentability: novelty and utility as defined in § 101 and § 102, and nonobviousness as defined in § 103. The first two sections express the traditional prerequisites of patentability that in this country date back at least to the Patent Act of 1790.[18] There is no dispute in this case

17. 66 Stat. 797, ch. 950 (codified at 35 U.S.C. §§ 100-293 (1976 & Supp. II 1978)).

18. Sections 101 and 102 provide respectively:

§ 101. Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

§ 102. Conditions for patentability; novelty and loss of right to patent

A person shall be entitled to a patent unless —

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this

(footnote continued on next page)

regarding utility or the novelty of cephalexin. Rather, Premo's primary contention is focused on the nonobviousness requirement of § 103, which was explicitly added to the patent laws in 1952.[19]

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country on an application filed more than twelve months before the filing of the application in the United States, or

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or

(f) he did not himself invent the subject matter sought to be patented, or

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

35 U.S.C. §§ 101 & 102 (1976). For a discussion of the historical development of the novelty and utility requirements, see Graham v. John Deere Co. 383 U.S. 1, 5-12 (1966); Kitch, Graham v. John Deere Co.: *New Standards for Patents*, 1966 Sup. Ct. Rev. 293, 303-30.

19. Patent Act of 1952, 66 Stat. 797, ch. 950. In Hotchkiss v. Greenwood, 52 U.S. (11 How.) 248 (1851), the Supreme Court formulated a definition of the "new" requirement of § 101 that has been recognized as the forerunner of the nonobviousness requirement. In striking down a patent that involved a mere substitution of materials—porcelain or clay for wood or metal in door knobs—the Court held:

> unless more ingenuity and skill in applying the old method of fastening the shank and the knob were required in the application of it to the clay or porcelain knob than were possessed by an ordinary mechanic acquainted with the business, there was an absence of that degree of skill and ingenuity which constitute essential elements of every invention.

Following the enactment in 1952 of § 103, there was an extensive academic debate on the question whether Congress intended to make the patentability standard less stringent than the *Hotchkiss* test. *Compare, e.g.*, Note, *The Standard of Patentability—Judicial Inter-*

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Section 103 provides:

> Conditions for patentability; non-obvious subject matter
>
> A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.[20]

Although the ultimate question of validity is one of law,[21] the Supreme Court has stated that the determination of obviousness entails several factual inquiries. *In Graham v. John Deere Co.*,[22] the Court held that under § 103

> the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.[23]

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pretation of Section 103 of the Patent Act, 63 Colum. L. Rev. 306, 310-12 (1963), *with, e.g.*, Note, *Patent Law—Test of Invention*, 1956 Wisc. L. Rev. 513, 514-17. The Supreme Court put an end to this debate in Graham v. John Deere Co., 383 U.S. 1 (1966), in which it held that Congress intended § 103 to codify the "judicial precedents embracing the *Hotchkiss* condition, with . . . directions that inquiries into the obviousness of the subject matter sought to be patented are a prerequisite to patentability." *Id.* at 17.

20. 35 U.S.C. § 103 (1976).

21. Great Atlantic and Pacific Tea Co. v. Supermarket Corp., 340 U.S. 147 (1950).

22. 383 U.S. 1 (1966).

23. *Id.* at 17.

In addition, the Court observed that

> such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.[24]

In cases dealing with the patentability of chemical compounds, the question of obviousness is particularly difficult because the differences between the molecular structure of the new drug and the prior art frequently are slight. Hence, the structure of the new compound may well be obvious when compared with the structure of related drugs that were in existence at the time the new drug was synthesized. Under these circumstances, if the patent law were to define a drug solely by its chemical structure, few new drugs would be patentable. As a consequence, the weight of authority—including every court of appeals that has addressed this question—holds that the structural obviousness of a new chemical compound does not, by itself, render the compound non-patentable. Instead, most courts have taken the view that the determination whether a new drug is nonobvious should be based on a consideration of the properties exhibited by the drug as well as the chemical structure of the drug.

The Court of Customs and Patent Appeals was the first appellate court explicitly to adopt this approach. That court's leading opinion on structural obviousness and § 103 is In re *Papesch*,[25] which involved the validity of a patent

24. *Id.* at 17-18.

25. 315 F.2d 381 (C.C.P.A. 1963).

on several trialkyl compounds. The hearing examiner had rejected the patent application on the ground that the new compounds were "obvious homologues of the methyl groups shown in the reference compound and the method of preparation [was] substantially the same."[26] The court held that although the new compounds were closely related chemically to the prior art, and therefore were structurally obvious, the drugs nevertheless were patentable. After reviewing a number of its own decisions,[27] in which "patentability was found . . . in spite of close similarity of chemical structure," the court declared:

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae, the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared. But a formula is not a compound and while it may serve in a claim to *identify* what is being patented, as the metes and bounds of a deed identify a plot of land, the *thing* that is patented is not the formula but the compound identified by it.[28]

The court concluded that "[t]here is no basis in law for ignoring any property in making such a comparison."[29]

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26. *Id.* at 382. "A homologue is a member of a series of compounds in which each member differs from the next member by a constant number of atoms." Commissioner of Patents v. Deutsche Gold-Und-Silber-Scheidenstalt Vormals Roessler, 397 F.2d 656, 661 n.13 (D.C.Cir. 1968). *See* R. Morrison & R. Boyd, Organic Chemistry 101 (2d ed. 1966).

27. *E.g., In re* Petering and Fall, 301 F.2d 676 (C.C.P.A. 1962); *In re* Lamboody, 300 F.2d 950 (C.C.P.A. 1962); *In re* Bergel, 292 F.2d 955 (C.C.P.A. 1961); *In re* Larsen, 292 F.2d 531 (C.C.P.A. 1961), *cert. denied,* 370 U.S. 936 (1962).

28. 315 F.2d at 391 (emphasis in original).

29. *Id.*

Patentability therefore depends on the outcome of a comparison of both the chemical and pharmacological properties of the old and new compounds.

In subsequent cases, the Court of Customs and Patent Appeals has reaffirmed and, perhaps, broadened the *Papesch* principle. In In re *Stemniski,*[30] it overruled the so-called *Hess-Henze* doctrine. The latter cases, decided before the passage of the Patent Act of 1952, held that the existence of a homologue was evidence that the new compound was obvious in light of prior art,[31] and that a presumption of obviousness arose where a homologue was disclosed in the prior art.[32] To rebut the presumption, an applicant must have demonstrated that "the claimed compound possesse[d] nonobvious or unexpected beneficial properties not actually possessed by the prior art homologue."[33] In *Stemniski,* the structures of the tin compounds at issue were very similar to the structures known to exist in the prior art. Under the principle set forth in *Hess* and *Henze,* the court observed, the petitioner had the burden of rebutting the presumption of obviousness. But "*Henze,* its predecessors and its progeny," the court asserted, "have met with their share of criticism over the years, both in this court, in other courts and elsewhere."[34] The court believing that "progress in the useful arts is ill-served by denying patents to inventors in the circumstances

30. 444 F.2d 581 (C.C.P.A. 1971).

31. *In re Hess,* 141 F.2d 122, 125 (C.C.P.A. 1944).

32. *In re Henze,* 181 F.2d 196, 201 (C.C.P.A. 1950).

33. *Id.* (emphasis added).

34. 444 F.2d at 587 (footnote omitted).

at bar," rejected the *Hess-Henze* rule.[35] In its stead, it held that structural similarity, or the existence in the prior art of a homologue, merely establishes a prima facie case of obviousness.[36]

In other decisions, the Court of Customs and Patent Appeals has suggested that the existence of but one unexpected property is enough to establish nonobviousness. For example, in In re *Ackerman*,[37] the prior art disclosed homologues of the claimed compound and provided the suggestion for modifying the homologues to obtain the compound at issue. Following synthesis, however, the new compound was found to be superior as an optical brightener in comparison with the prior art homologues. Inasmuch as the evidence demonstrated that this trait was unexpected, the court concluded, the new compound was nonobvious:

> The mere fact that such evidence deals with only one of a spectrum of properties possessed by that subject matter does not detract from its relevance. As we alluded to earlier, such evidence tends to prove that the subject matter claimed possesses a difference in properties over that with which it was compared which would have been unexpected. As such it is relevant and, we feel, convincing of unobviousness.[38]

One commentator has suggested that after *Ackerman* and its successors "it is evident that the court of patent appeals

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35. *Id.* (emphasis added).

36. *Id.* at 585.

37. 444 F.2d 1172 (C.C.P.A. 1971).

38. *Id.* at 1176. *In re* Merchant, 575 F.2d 865 (C.C.P.A. 1978); *Accord, In re* Albrecht, 514 F.2d 1389 (C.C.P.A. 1975); *In re* Langer, 465 F.2d 896 (C.C.P.A. 1972); *In re* Murch, 464 F.2d 1051 (C.C.P.A. 1972).

often regards the demonstration of significant unexpected properties as almost conclusive proof of nonobviousness.''[39]

The other two courts of appeals that have considered the question of structural obviousness and § 103 have adopted the *Papesch* doctrine. In *Commissioner v. Deutsche Gold-Und-Silber-Scheideanstalt Vormals Roessler,*[40] the issue was whether an ammonia-derivative compound which was selected from a group of compounds described by a general formula was patentable. The applicant had introduced evidence that the new compound possessed novel vermicidal properties that were not disclosed or suggested in the prior art and demonstrated that the new compound was more effective than the prior art as an intermediate in the production of patented sedatives and antihistamines. The Court of Appeals for the District of Columbia Circuit, speaking through Judge (now Chief Justice) Burger, articulated four reasons for adopting *Papesch.* First, it construed the Supreme Court's admonition in *Graham,* that a determination of obviousness should depend on ''several basic factual inquiries,'' as directing the courts to look to the relative properties of the new compound and the prior art, as well as to their comparative structures.[41] Second, there exist few compounds whose molecular structure is unknowable prior to their synthesis. The court reasoned that, were it to reject *Papesch,* ''few pharmaceutical compounds . . . [would] be patentable, and the incentive aspect of the patent system, which is basic, . . . be lost from an

39. Note, *Standards of Obviousness and the Patentability of Chemical Compounds,* 87 Harv. L. Rev. 607, 612 (1974).

40. 397 F.2d 656 (D.C. Cir. 1968).

41. *Id.* at 662 (quoting *Graham,* 383 U.S. at 17).

important area.''[42] Third, the court observed that the Patent Office traditionally permitted applicants to prove nonobviousness with evidence that the product possessed novel properties. Fourth, the court recognized that another patentability provision, § 101, focuses on ''what the compound will do, and its properties are of prime consideration'' for this purpose.[43] Accordingly, it held that the district court correctly considered all properties of the claimed compound in assessing its obviousness.

In another case involving Eli Lilly, the Court of Appeals for the Fifth Circuit also adopted the *Papesch* rule. In *Eli Lilly and Co. v. Generix Drug Sales, Inc.*,[44] Eli Lilly sought preliminarily to enjoin Generix from infringing the patent it owned on a synthetic morphine analgesic compound. The court rejected what it termed a ''stultifying per se rule of chemical similarity,'' and held that Eli Lilly was permitted to introduce evidence that the patented compound exhibited unexpected, nonobvious differences from the prior art. A rule banning the patentability of structurally obvious chemical compounds, in the court's view, would be inconsistent with the purposes of the patent laws if applied to the modern drug industry:

> In the field of drug patents today therapeutic value, not chemical composition, is the substance of all incentive to invent. Except where the state of the medical art and the state of the chemical art have been advanced and coordinated to the point that it is possible for the mind to conceive or predict with some minimal reliability a correlation between chemical analogues, homologues or isomers and their therapeutic value,

42. 397 F.2d at 663.

43. *Id.*

44. 460 F.2d 1096 (5th Cir. 1972).

> reason compels us to agree that novelty, usefulness and non-obviousness inhere in the true discovery that a chemical compound exhibits a new needed medicinal capability, even though it be closely related to structure to a known or patented drug. When such a fresh, efficacious, undisclosed use is identified, its inventor deserves the full ambit of statutory protection.[45]

Anything short of full patent protection for structurally obvious, but biologically nonobvious, new drugs that meet the other statutory criteria, according to the court, "would discourage both the inspiration-perspiration process of the laboratory and the incentive to publicly disclose products of value to mankind."[46]

We too are persuaded that, in determining whether a new drug meets the nonobviousness requirement of § 103,

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45. *Id.* at 1103.

46. *Id.* The Court of Appeals for the Second Circuit has twice been presented with the question regarding structural obviousness and § 103, but has elected both times to dispose of the cases on alternative grounds. *See* General Tire & Rubber Co. v. Jefferson Chemical Co., Inc., 497 F.2d 1238 (2d Cir.), *cert. denied*, 419 U.S. 968 (1974); Carter-Wallace, Inc. v. Otte, 474 F.2d 529 (2d Cir. 1972), *cert. denied*, 412 U.S. 929 (1973). In a recent extensive opinion, Judge Weinfeld appeared to adopt the *Papesch* rule. Warner-Jenkinson Co. v. Allied Chemical Corp., 477 F. Supp. 371, 393 (S.D.N.Y. 1979) (upholding patentability because "the essential unpredictability of the most important properties negates the claim of obviousness"). Two other district courts have specifically rejected *Papesch*. Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 341 F. Supp. 1303, 1333-35 (E.D.N.Y.) (dicta), *aff'd on other grounds sub nom.*, Carter-Wallace, Inc. v. Otte, 474 F.2d 529 (2d Cir. 1972), *cert. denied*, 412 U.S. 929 (1973); Monsanto Co. v. Rohm & Haas Co., 312 F. Supp. 778 (E.D. Pa. 1970) (dicta), *aff'd on other grounds*, 456 F.2d 592 (3rd Cir.), *cert. denied*, 407 U.S. 934 (1972). Judge Dooling's opinion in *Carter-Wallace* has met with considerable criticism. One group of commentators has even suggested that should the *Carter-Wallace* dictum become law, "it would literally sound the death-knell to patents on chemical compounds." 1 D. Dunner, J. Gambrell & I. Kayton, Patent Law Perspectives § A.1(1), at text accompanying note 190 (1980).

the district courts should consider all of the properties of the drug—including its structure, uses, and other traits—and compare those properties with their counterparts in the prior art. If the new compound, although structurally obvious, exhibits uses or traits that, at the time of their discovery, were not predictable to chemists or other persons skilled in the prior art, such differences indicate that the new compound is nonobvious for purposes of § 103. Whether the existence of an unexpected use or trait should conclusively establish nonobviousness, we need not decide at this time. If the unexpected property results in a substantial improvement over the prior art in respect to the therapeutic effectiveness or usefulness of the drug, however, it would appear to contravene the purposes of the patent laws to deny patentability on the basis of obviousness.[47]

The primary difficulty in ascertaining whether a new chemical compound is obvious is that most new compounds created today are the result of modification of an existing compound. Frequently, this modification is obtained through the use of a known method of synthesis. Hence, in synthesizing cephalexin, the Eli Lilly scientists modified cephaloglycin by substituting a methyl group for the side chain that attached to the cephaloglycin molecule at the 3-position of the nuclear ring. There is no claim that this type of modification was not obvious to other chemists working in the field at that time, or that the procedure was a

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47. *Cf*: Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 341 F. Supp. 1303, 1333-35 (E.D.N.Y.) (denying patentability in part because the pharmacological properties of the claimed compounds were not significant enhancements of the prior art), *aff'd on other grounds sub nom.*, 474 F.2d 529 (2d Cir. 1972), *cert. denied*, 412 U.S. 929 (1973).

difficult one. Thus, the structural composition of the cephalexin molecule might well be termed obvious in light of the prior art.

That a new compound such as cephalexin may be the end product of a fairly simple series of chemical reactions and structurally similar to a well-known prior-art compound such as cephaloglycin, however, does not necessarily imply that the synthesis of cephalexin itself was obvious. At the time cephalexin was first produced, chemists at Eli Lilly and other pharmaceutical companies were searching for a cephalosporin that would retain its potency when administered orally. The eighteen to twenty-two percent absorption rate of cephaloglycin permitted it to be administered orally, but its loss of ninety percent of its activity upon absorption prevented it from becoming a commercially effective oral antibiotic. Thus, industry chemists sought to synthesize a cephalosporin compound that would not lose so much of its activity upon absorption.

Eli Lilly chemists testified that they initially focused their attention on the substitution of the 3-methyl group for the side chain, but subsequently rejected this approach because the resulting compound displayed a markedly lower level of activity than cephaloglycin. As a result of the persistence of two chemists, Drs. Morin and Jackson, however, the Eli Lilly research group decided to renew experimentation using the 3-methyl group. The resulting compound—cephalexin—did not, as hoped for, retain a significantly high level of activity. Cephalexin did exhibit, however, the totally unexpected trait of one hundred percent absorption which made it the orally effective cephalosporin for which the chemists had been searching. This unexpected property therefore represented a substantial advancement over the prior art.

Under the circumstances, cephalexin may not reasonably be considered merely an obvious alteration of a previously known substance. At the time cephalexin was originally synthesized, the process of substituting a methyl group for the side chain occurring at the 3-position of a cephaloglycin nucleus was known and easily performable. It was not known, or expected by anyone other than Drs. Morin and Jackson, however, that this substitution would yield a compound that possessed the ultimate characteristic for which industry chemists were searching—that is, effectiveness as an oral antibiotic. Moreover, Drs. Morin and Jackson, who hoped that cephalexin would be such an antibiotic, expected that the salutary effects would occur as a result of the sustained activity of the new drug upon ingestion into the bloodstream. Even they did not consider, let alone anticipate, that cephalexin would be effective because of its one hundred percent absorption rate. Hence, the trait that made cephalexin the highly salutary drug that it is was neither expected by those skilled in the prior art nor anticipated by the chemists who synthesized it.

Section 103 authorizes the denial of patentability only if the "subject matter as a whole" was obvious in light of prior art, and provides that "[p]atentability shall not be negatived by the manner in which the invention was made."[48] The manner of producing cephalexin was readily predictable and performable, and therefore concededly obvious. But the real advancement over the prior art—cephalexin's one hundred percent absorption rate—was totally unexpected, even by the chemists who proposed its synthesis. Hence, taking cephalexin as a whole, we conclude that it was a nonobvious advancement over the prior

48. 35 U.S.C. § 103 (1976).

art. The lack of expectation or anticipation of the one hundred percent level of absorption, in our view, strongly indicates that the idea of creating the new componnd required a creative insight.[49]

This analysis is strengthened where, as here, the evidence demonstrates that previous attempts to synthesize a cephalosporin compound that performed satisfactorily as an oral antibiotic had exhibited a high degree of unpredictability. Chemists at Eli Lilly and other pharmaceutical companies had worked for years at refining the various cephalosporin compounds in order to obtain an effective oral antibiotic, but were stymied by the last step—finding a compound that would retain a sufficiently high combination of absorbability and activity upon absorption so that it could be produced in orally administrable doses. Against this background, the probability that the Eli Lilly breakthrough was unexpected or nonobvious in relation to the prior art is substantially enhanced.[50] Accordingly, we join our sister courts of appeals in holding that, in cases involving the patentability of chemical compounds, the determination of obviousness under § 103 should be based on a comparison of the structures of all properties possessed by the new compound and the prior art, including their respective structures, uses, and pharmacological traits. For this reason, the district court did not err in considering cephalexin's one hundred percent absorption rate during the course of its determination that cephalexin was nonobvious in light of the prior art.

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49. *See generally* Note, *supra* note 39, at 623-28.

50. *See In re* May, 574 F.2d 1082, 1094 (C.C.P.A. 1978).

2. Disclosure of the Nonobvious Trait

Premo's second contention on appeal is that the patent on cephalexin is invalid because Eli Lilly failed in its application or accompanying forms to disclose precisely the nonobvious trait.

Sections 111 and 112 of the code provide that all patent applications must be accompanied by

> A written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.[51]

The Court of Appeals for the Second Circuit, in *Norton Co. v. Bendix Corp.*,[52] reviewed the reasons underlying the disclosure requirement. It stated that § 112 has two primary purposes: (1) to require the patentee to make "a sufficient disclosure to enable one skilled in the art to reconstruct the invention"; and (2) to compel the patentee to "describe his invention with sufficient definiteness to enable others to discern the boundaries beyond which experimentation and invention are undertaken at the risk of infringement."[53] In *Carter-Wallace, Inc. v. Otte*,[54] the

51. 35 U.S.C. §§ 111 & 112 (1976).

52. 449 F.2d 553 (2d Cir. 1971).

53. *Id.* at 555.

54. 474 F.2d 529 (2d Cir. 1972), *cert. denied*, 412 U.S. 929 (1973).

court went on to declare that, in cases involving the patentability of structurally obvious chemical compounds, the disclosure standards should be particularly high because otherwise "the public will not obtain the benefit of the particular use which justified the grant of the patent."[55] In *Carter-Wallace,* the owner of the patent on the drug, meprobamate, sought to rely on its unexpected effectiveness as a tranquilizer to support its patentability. The court denied patentability under § 112 because "nothing in the specifications of the CIP application would have led the typical skilled worker in the art to use meprobamate as a tranquilizer."[56]

If the nature of the nonobvious trait "would inherently flow from the indicated use of the compounds," however, the Court of Customs and Patent Appeals has established that the requirements of § 112 are satisfied. Thus, in In re *Zenith,*[57] the patent owner sought to overcome a finding of structural obviousness by claiming that the new drugs exhibited a surprising separation of hypotensive and tranquilizing properties. The specification stated that the claimed compounds were useful as hypotensive agents, tranquilizers, antinauseants, antipyretics, and sedatives, but made no mention of the nonobvious separation of hypotensive and tranquilizing properties. For this reason, the Patent Office refused to consider the unexpected property, but the Court of Customs and Patent Appeals reversed. The court reasoned that the applicant had "disclosed a tranquilizer and subsequently established that if it is used as a tranquilizer it is a better one for it minimizes

55. *Id.* at 542.

56. *Id.*

57. 333 F.2d 924 (C.C.P.A. 1964).

the side effects of hypotensive activity."[58] Therefore, the court held that the compounds were patentable because "the advantage of minimized hypotensive activity would inherently flow from the indicated use of the compounds as tranquilizers."[59]

Similarly, in an abstract to the patent on cephalexin, which was added by amendment to the application prior to the issuance of the patent, Eli Lilly specified that cephalexin is "especially of interest for its use as an antibiotic when administered by the oral route." While the application was being processed, Eli Lilly also submitted a number of affidavits that specifically listed the oral ED_{50} values, as well as the M.I.C. values for cephalexin. The ED_{50} values, by which chemists measure oral effectiveness, showed that cephalexin is highly effective when administered orally. The M.I.C. values, by which chemists measure antibiotic potency, showed that cephalexin has a low activity level. Taken together, these data should have apprised chemists skilled in the art that cephalexin necessarily possessed an extremely high absorption rate. The data are part of the file history of the patent on cephalexin. Hence, although the application did not expressly identify the nonobvious trait—the one hundred percent rate of absorption—the information Eli Lilly did supply was such that the nature of the trait could readily be identified by a person skilled in the prior art. Under these circumstances, the nonobvious trait may be said "to flow inherently" from the properties and data supplied in the application and accompanying documents. Therefore, we conclude that Eli Lilly adequately complied with the disclosure requirements of § 112.

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58. *Id.* at 928.

59. *Id.* at 927. *Accord, In re* Khelghatian, 364 F.2d 870, 876 (C.C.P.A. 1966).

3. Introduction of New Matter by Amending the Patent Abstract

Section 132 of the code provides inter alia that "[n]o amendment shall introduce the disclosure of the invention."[60] Premo argues that Eli Lilly violated this provision by amending the patent abstract in 1968 to include the information discussed in part 2 above. The original application filed in 1962 disclosed only that cephalexin could be used as a topical sterilant.

In *Triax Co. v. Hartman Metal Fabricators, Inc.*,[61] the Court of Appeals for the Second Circuit provided the following definition of "new matter" as that term is used in § 132:

> An amendment to an application is not "new matter" within the Patent Act or Rules of the Patent Office unless it discloses "an invention, process or apparatus not theretofore described." . . . If the latter-submitted material accused of being "new matter" simply clarifies or completes the prior disclosure it cannot be treated as "new matter." . . . Moreover, the determination of the Patent office to admit the later-submitted material, thereby signifying that the Patent Office does not consider it to be "new matter," is presumptively correct.[62]

The 1968 amendment did not disclose an invention, process, or apparatus that was not described in the 1962 application. Rather, the 1968 amendment "completed" the prior disclosure by identifying and "clarifying" some of the properties of cephalexin, as well as its salutary performance

60. 35 U.S.C. § 132 (1976).

61. 479 F.2d 951 (2d Cir.), *cert. denied*, 414 U.S. 1113 (1973).

62. *Id.* at 956-57 (citations omitted).

as an oral antibiotic. Inasmuch as a chemical compound and its properties "are one and the same thing,"[63] newly discovered properties of the compound not disclosed in the original specification or abstract may be added by amendment without being treated as "new matter" under § 132.[64] Moreover, as in *Triax,* the decision of the Patent Office to admit the material contained in the amendment, which indicates that it did not consider the amendment to be "new matter," should be accorded substantial weight. Under these circumstances, we are not persuaded that the information contained in the 1968 amendment constituted "new matter" in violation of § 132.[65]

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63. *In re* Papesch, 315 F.2d at 391.

64. *Cf: In re Davies,* 475 F.2d 667, 672 (C.C.P.A. 1973) (affirming Patent Office's refusal to consider previously undisclosed unexpected properties, but authorizing refiling of application to incorporate such properties):

> Since the subject matter to be claimed in a subsequently filed application would be identical to that claimed here, the later application would be entitled to the benefit of the filing date of the application we now consider. See In re Kirschner, 49 CCPA 1234, 305 F.2d 897, 134 USPQ 324 (1962). We certainly do not think the newly disclosed properties alter the subject matter sought to be patented.

This procedure did not prejudice the applicant in *Davies* because a patent had not yet been granted. In contrast, were we to follow the *Davies* procedure here, Eli Lilly would suffer economic loss. *Davies* would appear to require that the patent be invalidated and Eli Lilly given leave to refile a more complete application until the new application was granted. Premo and other drug companies presumably would be free to sell cephalexin in the United States, because there would exist no valid patent prohibiting such sales.

65. Premo contends that disclosure of the usefulness of cephalexin as an oral antibotic for the first time in the abstract violated 37 C.F.R. § 1.72(b) (1979), which states in relevant part:

> The purpose of the abstract is to enable the Patent and Trademark Office and the public generally to determine quickly from

(footnote continued on next page)

4. Identification of All Inventors

Section 116 of the code provides that, "[w]hen an invention is made by two or more persons jointly, they shall apply for [a] patent jointly and each sign the application and make the required oath."[66] In *Amax Fly Ash Corp. v. United States*,[67] the Court of Claims held that if greater or fewer than the true number of inventors are named in the application, the patent is void.[68] "However, misjoinder or nonjoinder of inventors are technical defenses requiring clear and convincing evidence."[69]

Premo claims that Eli Lilly failed to comply with this requirement because the patent application listed only Drs. Morin and Jackson, while the one hundred percent absorption rate actually was discovered by the biochemist who tested cephalexin on human subjects in 1967. In support of this contention, Premo relies on *General Tire & Rubber Co. v. Jefferson Chemical Co.*[70] Jefferson was the assignee of a patent on certain types of polyurethanes, and

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a cursory inspection the nature and gist of the technical disclosure. The abstract shall not be used for interpreting the scope of the claims.

We disagree. The disclosure in the abstract did not broaden the claim or interpret the scope of the claim, which was and always has been for cephalexin. Instead, the abstract merely showed "the nature and gist of the technical disclosure" by disclosing that cephalexin was useful as an oral antibiotic.

66. 35 U.S.C. § 116 (1976).

67. 514 F.2d 1041 (Ct. Cl. 1975) (per curiam).

68. *Id.* at 1050 (citing Iowa State Univ. Research Foundation, Inc. v. Sperry Rand Corp., 444 F.2d 406, 408 (4th Cir. 1971)).

69. Id. (citing Garrett Corp. v. United States, 422 F.2d 874, 880 (Ct. Cl. 1970) (per curiam)).

70. 497 F.2d 1283 (2d Cir.), *cert. denied*, 419 U.S. 968 (1974).

General owned a virtually identical patent. The polyurethanes at issue were first synthesized by the assignor of the Jefferson patent. The polyurethane compounds were structurally obvious, however, in view of the prior art. Hence, in support of patentability, Jefferson sought to rely on several unexpected traits exhibited by the polyurethanes. The problem with this theory, according to the Court of Appeals for the Second Circuit, was that the unexpected traits were discovered not by Jefferson or its assignor, but by the assignor of the General patent. The court held that only General's patent was valid because its assignor was the true inventor. Judge Friendly, writing for the court, reasoned that "just as 'accidental results, not intended and not appreciated, do not constitute anticipation,' . . . so an unappreciated result of a structurally obvious modification cannot of itself constitute invention."[71]

After considering Premo's argument on this point, the district court dismissed the defense as "specious."[72] Although we believe that *General Tire* is colorable authority for the defense proffered by Premo, we are persuaded that it is distinguishable from the present action.

The compound whose patentability is at issue indisputably was synthesized by Drs. Morin and Jackson. They performed the synthesis with the hope that the resulting compound would be the effective oral antibiotic that cephaloglycin and other existing cephalosporins were not. Subsequent testing conducted by an Eli Lilly biochemist on human patients demonstrated that cephalexin was such a drug, although not for the reasons predicted by Drs. Morin

71. *Id.* at 1291 (citation and footnote omitted).

72. Eli Lilly & Co. v. Premo Pharmaceutical Laboratories, Inc., Civ. No. 78-2589, slip op. at 27 n. 14 (D.N.J. filed July 13, 1979).

and Jackson. Although we have held today that, in assessing the obviousness of a new drug under § 103, courts must consider all of the properties of the new compound, the fact that a person other than Dr. Morin or Dr. Jackson *discovered* the nonobvious trait possessed by cephalexin does not make that person an *inventor* of cephalexin for purposes of § 116. For it is without question that the named inventor, Drs. Morin and Jackson, were the only persons who performed the synthesis that created the patented product. In the words of § 116, cephalexin was "made by" the two named inventors, not by the biochemist who first noted that the organic chemists' predictions had been realized.

The concerns underlying the Second Circuit's decision in *General Tire* simply are not present here. In *General Tire,* the parties were two companies which each owned a patent for the same compound. The court invalidated Jefferson's patent, which was premised on an unexpected trait, because the original owner of the patent had been unaware of the existence of that trait. Instead, the unexpected trait was first discovered by the assignor of General Tire's patent. Faced with competing claims by companies that each had contributed to the advancement over the prior art—one by synthesizing the new compound, the other by discovering its unexpected trait—the court determined that the owner of the patent whose assignor most contributed to the advancement should have its claim of ownership sustained.

There are no analogous competing claims in this case. Both the synthesis of cephalexin and the discovery of its unexpected trait were conducted by chemists employed by Eli Lilly. In contrast, Premo contributed not at all to either the synthesis or the subsequent testing of cephalexin.

As such, there is not present here the equitable consideration which gave rise to the court's decision in *General Tire* —that is, to assign patent ownership to the party that contributed more to the advancement in the state of the art. By identifying Drs. Morin and Jackson as the "makers" of cephalexin, Eli Lilly complied fully with the requirements of § 116. Therefore, we hold that the district court did not err in rejecting Premo's defense in this respect.

5. Summary

The foregoing are the only contentions advanced by Premo in its challenge to the decision of the district court that Eli Lilly fulfilled all of the statutory requirements of patentability. We have concluded that the district court did not err in any of its conclusions in this regard. Hence, there is no occasion to address Premo's challenge to the district court's finding of industry acquiescence[73] on which the court relied as an alternative basis for its holding that the patent is valid. Accordingly, we turn to Premo's final

73. Acquiescence in the owner's patent rights in a commercially successful product by other members of the industry is generally recognized as circumstantial evidence that the patent is valid. Evidence that other firms paid royalties to the patent owner is a particularly strong indicium of validity. *See, e.g.*, Illinois Tool Works, Inc. v. Sweetheart Plastics, Inc., 436 F.2d 1180, 1187 (7th Cir.), *cert. dismissed*, 403 U.S. 942 (1971); *cf.* Carter-Wallace, Inc. v. Davis-Edwards Pharmacal Corp., 443 F.2d 867 870-75 (2d Cir. 1971), *cert. denied*, 412 U.S. 929 (1973) (industry acquiescence is a prerequisite to the issuance of a preliminary injunction).

The effect of acquiescence is to lessen the patentholder's burden of proof of validity, by creating a presumption of validity, for the purpose of obtaining a preliminary injunction. *See* 8 A. Deller, Walker on Patents § 688 (2d Ed. 1973). Inasmuch as we have sustained the district court's determination of patent validity based on direct technical evidence, the circumstantial evidence of acquiescence becomes irrelevant.

contention: that the district court abused its discretion in granting Eli Lilly's application for a preliminary injunction.

B. Preliminary Injunction

The standard in this Circuit for a preliminary injunction is well-settled. As we stated in *Constructors Association of Western Pennsylvania v. Kreps:*

> [T]his Court has consistently identified four factors which must be examined in ascertaining the propriety of a preliminary injunction: . . . the moving party must generally show (1) a reasonable probability of eventual success in the litigation and (2) that the movant will be irreparably injured *pendente lite* if relief is not granted. . . . Moreover, while the burden rests upon the moving party to make these two requisite showings, the district court "should take into account, when they are relevant, (3) the possibility of harm to other interested persons from the grant or denial of the injunction, and (4) the public interest." . . . While these factors structure the inquiry, however, no one aspect will necessarily determine its outcome. Rather, proper judgment entails a "delicate balancing" of all elements. On the basis of the data before it, the district court must attempt to minimize the probable harm to legally protected interests between the time that the motion for a preliminary injunction is filed and the time of the final hearing.[74]

74. 573 F.2d 811, 814-15 (3rd Cir. 1978) (citations and footnotes omitted). *Accord,* Continental Group, Inc. v. Amoco Chem. Corp., 614 F.2d 351, 356-57 (3rd Cir. 1980); Fitzgerald v. Mountain Laurel Racing, Inc., 607 F.2d 589, 600-01 (3rd Cir. 1979), *cert. denied,* 48 U.S.L.W. 3746 (U.S. May 20, 1980); A. O. Smith Corp. v. FTC, 530 F.2d 515, 525 (3rd Cir. 1976); Delaware River Port Auth. v. Transamerican Trailer Transport, Inc., 501 F.2d 917, 919-20 (3rd Cir. 1974).

In reviewing the grant or denial of a preliminary injunction, we must affirm the order of the district court unless the court abused its discretion, committed an error of law, or seriously misjudged the evidence.[75]

Premo concedes that, if the patent on cephalexin is valid, the owner of the patent is Eli Lilly and Premo would infringe the patent were it to sell cephalexin in the United States market. Inasmuch as we have concluded that the district court did not err in holding that the patent is valid, it is virtually certain that Eli Lilly will succeed on the merits of its claims for declaratory and permanent injunctive relief. Thus, the first factor, probability of eventual success in the litigation, weighs heavily in favor of the decision to grant the preliminary injunction.

The district court also concluded that Eli Lilly would suffer irreparable harm if the preliminary injunction were not granted. It noted that Premo was in Chapter XI reorganization in 1973, reported profits of only $2 million in 1978, and is currently being sued by four other pharmaceutical companies for patent infringement. The court reasoned that, inasmuch as Eli Lilly's annual sales of cephalexin exceeded $100 million, "damages could very conceivably run beyond Premo's ability to pay them."[76] Moreover, the court found that it was common in the pharmaceutical industry for other generic producers to enter the market whenever the patent on a commercially successful drug was challenged. In view of this evidence, the second factor—irreparable injury—also supports the district court's decision. The possibility of harm to other interested persons

75. Glasco v. Hills, 558 F.2d 179, 180 (3rd Cir. 1977).

76. Eli Lilly & Co. v. Premo Pharmaceutical Laboratories, Inc., Civ. No. 78-2589, slip op. at 26 (D.N.J. filed July 13, 1979).

does not appear to be relevant to the issues in this case. No such person or corporation has been brought to the Court's attention.

The district court concluded that the fourth factor, the public interest, also weighed in favor of Eli Lilly. Although Premo claims that it would serve the public interest by selling cephalexin at a significantly lower price than Eli Lilly, this does not necessarily establish that it would be in the public interest to permit it to do so.

In enacting the patent laws, Congress recognized that it is necessary to grant temporary monopolies on inventions in order to induce those skilled in the "useful arts" to expend the time and money necessary to research and develop new products and to induce them "to bring forth new knowledge."[77] This justification for sacrificing short-term price competition in order to foster creativity and improvement of products in long-run is particularly applicable to the pharmaceutical industry.

As the record in this case indicates, the development and perfection of new drugs frequently requires the devotion of years of research time and the expenditure of millions of dollars. For example, it took Eli Lilly twenty years to develop cephalexin, during which time its investment in research and testing exceeded $10 million. Each year, Eli Lilly spends approximately ten percent of its net sales revenue on research and development; in 1978,

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77. Graham v. John Deere Co., 383 U.S. 1, 9 (1966). The Constitution provides Congress the power "[t]o promote the Progress of Science and the useful Arts, by Securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const. art. I, § 8, cl.8. The current patent laws accord the patentee, his heirs, or assigns, the exclusive right to manufacture, to use, or to sell the patented items for a period of seventeen years. 35 U.S.C. § 154 (1976).

such expenditures exceeded $140 million. Unless this type of an investment of human and capital resources is rewarded by some form of patent protection, companies such as Eli Lilly might well choose not to undertake such large expenditures and instead devote themselves to other endeavors. To the extent this occurs, resources would be diverted from activity that is socially beneficial—the development of new drugs. As one commentator has put it, "Viewed in these terms, the patent grant . . . functions as a means of raising the expected return to be gained from basic drug research sufficiently to overcome the investor firm's risk aversion and induce it to invest additional funds in research instead of alternative investment opportunities such as production process improvement programs, advertising, increased customer service, or the like."[78]

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78. Note, *supra* note 39, at 619 n.54.

Long-term investment in research and development is the primary means by which a highly industrialized economy such as ours continues to grow, to maintain its share of international trade, and thereby to provide employment for its citizens. One observer has defined the dangers of diminishing investment in the inventive and innovative arts in the following terms:

> Research and development is by definition a long-range thing. The gestation period of an idea from cerebral conception to profit-making reality is from five to 20 years. Furthermore, not every idea is brought to economic fruition. For every one that does make it to the marketplace, 99 wither along the way, oftentimes after years of research and expense that must be written off.
>
> Yet despite these slim chances of success, American industry has willingly invested its corporate profits in R&D, and with good reason: In times of economic stability, the risks were considered reasonable, and the investments turned handsome profits. It was simply a matter of good business sense, the happy consequence of which was a national industry, technology, society and wealth that became the envy of the world.
>
> In times of double-digit inflation such as these, however, that very same good business sense looks for other ways to invest its

(footnote continued on next page)

Thus, Premo's claim that the public interest would be served by permitting it to enter the cephalexin market and sell at a lower price than currently offered by Eli Lilly is contrary to Congress' purposes in enacting the patent laws. Although companies such as Premo, which do not engage in significant amounts of research and development, consequently might be able to undercut the prices offered by pharmaceutical manufacturers that devote large sums to invention and product improvement, this type of short-term competition does not, at least in the considered opinion of the Congress, serve the public interest. Instead, Congress has determined that it is better for the nation in the long-run to afford the inventors of novel, useful, and non-obvious products short-term monopolies on such products than it is to permit free competition in such goods. Therefore, the fourth factor—whether the public interest would be better served by denying or granting the preliminary injunction—also supports the district court's decision.

In sum, all three considerations pertinent to the decision of the district court to grant the preliminary injunction, weigh in favor of that result. Eli Lilly has demonstrated a high probability of success on the merits, the record indicates that Eli Lilly would be irreparably harmed were the preliminary injunction not issued, and the decision to grant the preliminary injunction would serve the public

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capital for maximum growth. Long-range investments in R&D are no longer attractive when inflation chomps away at any potential return. Thus American business hedges, growing not by expansion through the development of innovative products but by merger and acquisition.

Letter from A. J. Scarpellino, Jr., senior engineer at the Inco Research and Development Center, Sterling Forest, N.Y. to the editor of the *New York Times*, N.Y. Times, June 20, 1979, § A at 22, col. 3.

interest as it has been defined by Congress. Accordingly, we hold that the district court did not abuse its discretion in preliminarily enjoining Premo from manufacturing or selling cephalexin on the domestic market.

The judgment of the district court will be affirmed.

A True Copy:

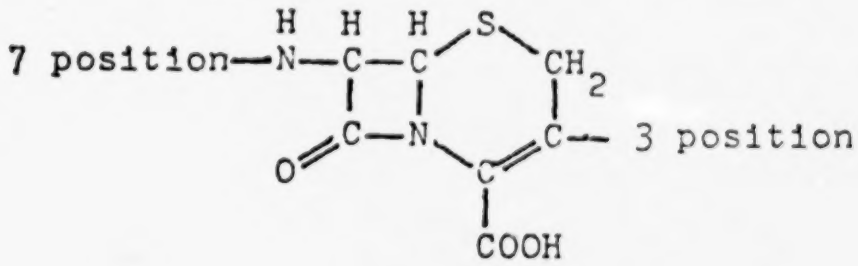
Teste:

Clerk of the United States Court of Appeals for the Third Circuit

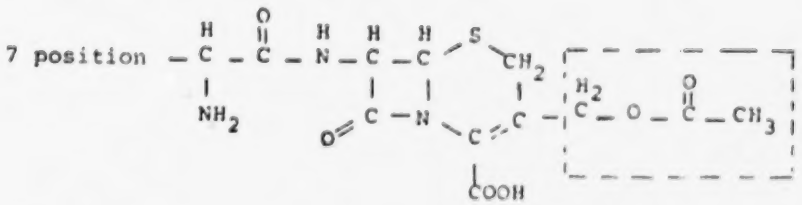
APPENDIX

APPENDIX

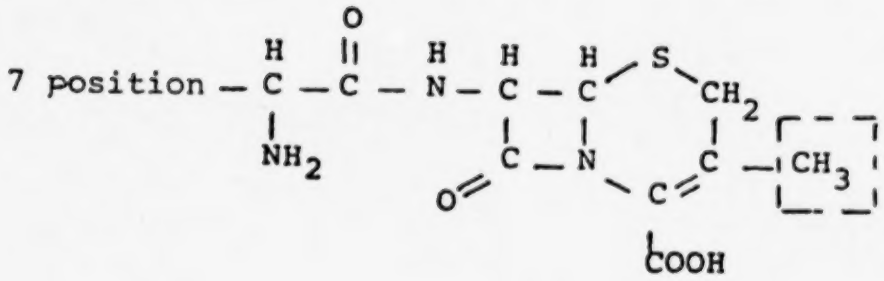
The common structural characteristic of all cephalosporins is the nucleus, which consists of a 4-membered beta-lactem ring fused to a 6-membered thiazine ring with a double bond between the 3- and 4-positions:



The various cephalosporins differ from one another in the type of side chain attached to the 7-position and in the type of substituent attached to the 3-position. Thus, cephaloglycin possesses an acetoxymethyl group, which is attached to the 3-position of the nucleus:



In contrast, cephalexin possesses a plain methyl group attached to the 3-position:



It is this structural change that produces the pharmacological differences between the two compounds.

APPENDIX B

Opinion of the United States District Court for the District of New Jersey July 13, 1979

(not officially reported)

UNITED STATES DISTRICT COURT

DISTRICT OF NEW JERSEY

Civil Action No. 78-2589

ELI LILLY AND COMPANY,

Plaintiff,

v.

PREMO PHARMACEUTICAL LABORATORIES, INC., *et al,*

Defendants.

OPINION

MEANOR, *District Judge*

The facts of this case parallel those of *Zenith Labs. Inc.*, v. *Eli Lilly*, 460 F. Supp. 812 (D.N.J. 1978), which should be read as an introduction to this opinion. Premo, like Zenith, is a generic house that does no or minimal research and development. Similarly, Premo concedes it is infringing a Lilly patent. However, it contends the patent is invalid due to obviousness. The only significant difference in the case is that in *Zenith* the motion was for a preliminary injunction against infringement of the '656 Patent as opposed

to the '861 Patent. The present case involves only the '861 Patent. The '861 Patent is for cephalexin, an effective oral antibiotic. The '656 Patent is on the dense form of cephalexin. This dense form makes cephalexin marketable because it is more manageable and, therefore, can be easily capsulized. However, it is important to keep in mind that the '861 Patent is a necessary underlying patent of the '656 Patent.

The following history of the development of the '861 and '656 Patents is drawn from *Zenith*.

> The cephalosporins are a family of antibiotic drugs derived from material produced by the fungus *Cephalosporium acremonium*. Cephalosporin-C, the parent compound from which the drug family was developed, was first isolated by British scientists in the 1950s. As a group the cephalosporins possess a number of properties which make them unusually effective as antibiotics. Bacteria are commonly classified in accordance with whether they take or reject a so-called Gram stain, named after the scientist who discovered the classification test. Those which take stain are termed gram-positive; those which reject it, gram-negative. While penicillin, a comparable antibiotic, is active against only gram-positive bacteria, the cephalosporins are effective against both gram-positive and gram-negative strains. Cephalosporins also have low toxicity and allergenicity, producing relatively few adverse side effects and allergic reactions. One consequence of this is that cephalosporins may sometimes be used to treat penicillin-allergic individuals. (Abraham Affidavit 1-3; Flynn Affidavit 3-4).
>
> In terms of chemical structure, the members of the cephalosporin family have in common a central structural nucleus formed of a 6-membered ring of 7-amino-

cephalosporanic acid (7-ACA). The various cephalosporins differ from one another in the number and type of side chains attached to the nucleus. While the family members have approximately the same range of antibiotic activity and toxicity, their structural differences result in variant pharmacological properties, that is, differing chemical behavior in the body.

In the early 1960s, British scientists discovered a method to isolate 7-ACA nucleus and add various side chains to create a variety of cephalosporins with activity more potent than Cephalosporin-C. However, the methods used were not practicable for the production of cephalosporins on a commercial scale. About this time the National Research Development Corporation, a crown corporation of Great Britain founded to assist in the commercialization of the inventions of British subjects, became involved in promoting cephalosporin research. It concluded agreements with a number of pharmaceutical companies whereby the companies committed themselves to participate in cephalosporin research and to turn over their findings to the corporation in exchange for access to prior research results and other technical aid. Lilly and at least seven other laboratories in several countries agreed to embark on this research effort. (Flynn Affidavit 4).

Lilly was the first to develop an efficient method of producing 7-ACA nucleus, and by early 1962 Lilly's first cephalosporin antibiotic was ready for clinical trials. (Flynn Affidavit 5-8).

By the end of 1970, Lilly had put three cephalosporin products on the market. Cephalothin, introduced in 1964 under the trademark Keflin, and cephaloridine, introduced in 1968 under the trademark Loridine, are effective only when administered by injection because they are not sufficiently absorbed in the body when

given orally.[2] Cephaloglycin, introduced in 1970 under the trademark Kafocin, was Lilly's first oral cephalosporin. Cephaloglycin was found to be 18 to 22% absorbed into the bloodstream upon ingestion, a percentage sufficient to make it a satisfactory oral drug. However, cephaloglycin has reduced activity in comparison with other cephalosporins. This is so because upon ingestion about 90% of the cephaloglycin dose is converted by a chemical reaction into a related compound. This compound has gram-positive activity about equal to that of cephaloglycin, but its gram-negative activity is substantially lower. (Van Heyningen Affidavit 2-3).

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2. Some of the facts about Keflin and Loridine are drawn from the findings of fact of Judge Higginbotham in *SmithKline Corp.* v. *Eli Lilly and Co.*, 472 F. Supp. 1089 (E.D. Pa. 1976), *aff'd*, 575 F.2d 1056 (3d Cir. 1978), an antitrust action involving the marketing of cephalosporins.

In an effort to find an oral cephalosporin which would not undergo the chemical changes exhibited by cephaloglycin, Dr. Robert E. Morin and Dr. Billy G. Jackson, researchers at Lilly, proposed modifying cephaloglycin by substituting a methyl group for the side chain attached to the cephaloglycin molecule at position 3 on the nuclear ring. The resulting compound is known as cephalexin.

Clinical studies of cephalexin demonstrated that, unlike cephaloglycin, the compound underwent no chemical changes upon ingestion, and thus retained its gram-negative activity when given orally. In addition, cephalexin was found to be 100% absorbed from the gastrointestinal tract, and to be completely excreted in the urine without chemical alteration. (Van Heyningen Affidavit 3-4; Griffith Affidavit 4). Thus, cephalexin, one of a group of compounds called 3-methyl-cephalosporins, is highly satisfactory for oral administration.

On September 14, 1966, Morin and Jackson applied for a patent on their discovery of the usefulness of

various 3-methyl-cephalosporin compounds as oral antibiotics. The '861 Patent was subsequently issued on April 21, 1970. Cephalexin is one of the compounds included within this patent.

Morin and Jackson also developed a process for the generation of cephalosporins from penicillin. Cephalexin can be manufactured by this method. (Van Heyningen Affidavit 4-5). This Morin-Jackson process is the invention claimed in United States Patent No. 3,275,626, entitled "Penicillin Conversion Via Sulfoxide," of which the '861 Patent is a continuation in part.

The '656 Patent.

While cephalexin was known to be effective for oral administration, it could not be marketed in the forms in which it was originally produced. It was first crystallized from water at room temperature as a dihydrate, that is, as a crystal containing two molecules of water per molecule of cephalexin. The dihydrate crystals so formed are characteristically small, fluffy and fiber-like, and they are so bulky that a full dose cannot be put into a single capsule of acceptable size. On drying, the dihydrate crystals convert readily into monohydrate crystals by the loss of a single molecule of water per molecule of cephalexin in the crystalline structure. However, the monohydrate so formed is likewise fluffy, and the crystals tend to pick up static charge and become "flyaway," making handling and encapsulation impractical on a commercial basis.

Lilly research efforts were directed towards the modification of the crystallization process to generate a more manageable product. While crystallization had originally been conducted at low temperatures to reduce the danger of degradation of the cephalexin, Earl Van Heyningen proposed that crystallization be tried at elevated temperatures. It was discovered that at

temperatures of about 60° C. or above, cephalexin monohydrate could be crystallized directly, and the crystals so obtained were relatively large, non-hygroscopic, dense and non-electrostatically excitable. Further, a single dose would fit into a capsule of acceptable size. (Van Heyningen Affidavit 6-7).

On April 21, 1969, Van Heyningen filed an application with the Patent Office on this dense form of cephalexin monohydrate (hereinafter sometimes referred to as DCM). The '656 Patent, here at issue, ultimately issued on April 11, 1972.

The patent contains two independent claims as to the crystalline product taught therein. DCM is said to have unique x-ray diffraction properties and its density is said to fall within the range of 0.50 to 0.60 g./ml. The term density is nowhere defined in the patent. Lilly has admitted that all forms of cephalexin monohydrate have the same x-ray diffraction pattern. (Lilly's Answer to Zenith's Interrogatory No. 22).

460 F. Supp. at 814-816.

Most of the facts relevant to a consideration of patent validity based on industry acquiescence are set forth in *Zenith*. The following is drawn from that case.

Lilly's Commercial Production Of Keflex.

Before human clinical research can be done on a new drug, an investigational new product application must be submitted to the Food and Drug Administration. Lilly filed such an application for DCM in early 1967 and commenced funding clinical work in 1968. The Food and Drug Administration approved the drug for marketing in early 1971. (Christensen Affidavit 2).

Lilly markets DCM under the trademark of Keflex.

Since 1958 a substantial portion of the time and money allocated to research at Lilly's laboratories has been devoted to work on cephalosporins. Ten million dollars was invested in research and development on

Keflex. The research activities funded by this sum included chemical synthesis, laboratory evaluations *in vitro* and *in vivo*, development of analytical methods, development of dosage forms, stability testing, toxicology, development of processes for the production and purification of cephalexin monohydrate as a chemical product, animal and human pharmacology and metabolism studies and human clinical evaluations. (Herr Affidavit 2). Of that $10 million, Lilly spent over $1.8 million on human clinical studies from 1968 to mid-1977. The purpose of these studies was to attempt to confirm the activity of cephalexin monohydrate observed in laboratory and animal studies in human subjects, to examine and assess the nature and extent of toxicity of the drug upon human administration, to establish appropriate dosage levels, to determine any incompatibilities or contraindications that would suggest precautions to be observed in the use of the drug, and to identify the clinical conditions for which the antibiotic could appropriately and safely be prescribed. A substantial portion of this money was used to fund studies necessary to obtain FDA approval to market the drug. However, more than half was expended after Keflex was put on the market. Post-marketing studies are designed to gain additional information on the drug's activity under normal usage, to answer questions which arise in the course of such usage, and to explore avenues for extending the safeness and usefulness of the drug. Lilly indicates that it continues and will continue to do such work on Keflex in the future. (Christensen Affidavit 2-3).

In order to launch Keflex into the drug market once it was approved by the FDA, Lilly conducted a variety of promotional activities directed at physicians. Information about the drug was conveyed by product samples, medical literature, symposiums

and advertising. During the first two years that Keflex was marketed, Lilly spent approximately $12.3 million on such promotion. (Step Affidavit 5).

Since its introduction in 1971, Keflex has experienced substantial commercial success. Yearly sales have increased since 1971 to a high of over $80 million in 1976.[1] It appears that Keflex or cephalexin monohydrate is the most widely prescribed oral cephalosporin in the United States today. (Whale Affidavit 2; Kirby Affidavit 2). Cephaloglycin, Lilly's prior oral cephalosporin drug, is of little general use today because of its relatively poor absorption in the body and its low blood levels, although the drug remains a drug of choice for certain applications, such as urinary tract infections. As against ampicillin, an oral penicillin, cephalexin monohydrate also compares favorably on account of its greater absorption rate and its suitability for penicillin-allergic patients. (Kirby Affidavit 2). Cephalexin monohydrate has obvious advantages over injectable antibiotic cephalosporins where oral administration is not contraindicated in that it may be administered without the stress and expense of injection, and it is suitable for outpatient treatment. (Herr Affidavit 3).

The Drug Industry And The '656 Patent.[2]

Lilly has asserted that the pharmaceutical industry in the United States is competitive both in the areas of technological and scientific invention and marketing (Whale Affidavit 2; Step Affidavit 2); that companies within the industry are experienced in the management of patent rights, and that competition promptly appears when the patent on a commercially successful pharmaceutical product expires or appears

1. Lilly reported sales of over $100 million in 1978. (Updated Whale Affidavit).

2. These facts apply equally to the '861 Patent. The '861 Patent is a necessary underlying patent of the '656 Patent.

to be invalid. (Whale Affidavit 2). Zenith does not dispute this characterization of the industry, although it suggests that at least with respect to the '656 Patent there are factors which would militate against challenges of said patent even if it were perceived to be invalid. Zenith's position as to the inferences that may be drawn from the failure of any drug company to challenge the '656 Patent will be addressed *infra*, n. 7. I conclude that Lilly's uncontested characterization of drug industry competition is accurate.

In 1972, the '656 Patent was issued to Lilly as assignee of the inventor, Earl M. Van Heyningen, and at all times since issuance, Lilly has been its owner.

Until Zenith's entry into the market, five and a half years after issuance of the '656 Patent, Lilly was the sole source of cephalexin monohydrate in the United States. The absence of entrants other than Lilly into the United States market during the period was not a reflection of a dearth of drug industry interest in the manufacture and sale of cephalexin monohydrate. During that period, two small United States pharmaceutical companies sought licenses to make the drug, but Lilly denied their requests. (Whale Affidavit 2-3).

Four multi-national drug companies which manufacture the drug in foreign countries or have the capacity to manufacture it here have respected Lilly's '656 Patent and refrained from entering the United States DCM manufacturing or sales market.[3] Bristol-Myers manufactures DCM in Lativa, Italy, and sells in Italy and other countries where Lilly has no patent. In 1975, Bristol-Myers produced some 15-20 tons of the antibiotic. (Whale Affidavit 3; Whale Affidavit of March 7, 1978 (hereinafter Whale Supplemental

3. It should be noted that unlike Zenith, Premo has submitted depositions stating that the major drug companies Lilly alleges acquiesced did not have any interest in marketing cephalexin in the United States. (Kaczmarek Dep.; Lourie Dep.)

Affidavit) 2). Glaxo Group, Ltd. and its affiliate, Ankerfarm, manufacture DCM in England and market it in foreign countries under license from Lilly. In 1975, Glaxo and Ankerfarm manufactured about 35-50 tons of the drug which it sells under the trademark Ceporex. There is no express or implied provision in the Glaxo licenses or other Lilly-Glaxo agreements whereby Glaxo would lose its license right to manufacture, use and sell DCM in foreign countries if Glaxo were to infringe the '656 Patent. (Whale Affidavit 3; Whale Supplemental Affidavit 2-3).

E.R. Squibb and Sons and SmithKline Corporation both manufacture and sell cephradine, a product which is closely related in chemical structure to DCM. Cephradine and DCM are made from identical starting materials and by nearly identical processes. The only difference in their manufacture is that in making cephradine, one of the starting materials must be subjected to a preliminary chemical conversion to a closely related intermediate. To the extent said conversion is incomplete, the unconverted starting material becomes cephalexin in the cephradine product. (Hatfield Affidavit 2). Both SmithKline and Squibb have royalty-bearing licenses under the '656 Patent for the inclusion of up to 10% cephalexin in their cephradine product. Cephradine is manufactured by SmithKline in Swedeland, Pennsylvania and by Squibb in Humacao, Puerto Rico. Each company produced about 15 tons of cephradine in 1975. SmithKline and Squibb have the present capacity to manufacture and sell DCM in the United States, and their entrance into the United States DCM market would not be grounds for Lilly to terminate their license rights under the terms of their respective licenses or any other agreements. (Whale Supplemental Affidavit 4-5).

460 F. Supp. at 816-818.

There must be a separate statement of the technical facts relevant to a consideration of Section 103 "obviousness" because the prior art and the claimed compound in this case differ from those in the *Zenith* case. *See* 35 U.S.C. § 103.

Premo contends that four compounds are prior art and cephalexin is obvious in light of this prior art. In terms of chemical structure, cephalexin has the central nucleus common to the cephalosporins, 7-aminocephalosporanic acid (7-ACA). It has a methyl group at the 3 position and a phenylglycine side chain at the 7 position. In terms of properties, cephalexin, like most cephalosporins, is effective against both gram-negative and gram-positive bacteria. It also exhibits 100% absorption in the gut. (Flynn Affidavit; Van Heyningen Affidavit.)

The first prior art compound that Premo urges made cephalexin obvious is cephaloglycin.[4] It consists of the basic cephalosporin nucleus with the naturally occurring acetoxymethyl group at the 3 position and a phenylglycine side chain added at the 7 position. (Tr. 135) In terms of properties, it is absorbed in the gut to the extent of about 20%. (Tr. 306) It is not effective against gram-negative bacteria because the acetyl portion of the acetoxymethyl group at the 3 position deacetylates *in vivo*. The difference between cephaloglycin and cephalexin is that cephalexin contains a methyl group instead of the acetoxymethyl chain at the 3 position. There was no reason to believe that replacing the acetoxymethyl group with methyl would

4. Cephaloglycin, which Lilly markets under the trademark Kafocin, was invented by Dr. R.B. Morin, one of the two inventors of cephalexin, and is covered by U.S. Patent No. 3,560,489.

result in greater absorbability. The reason for the replacement was to avoid deacetylation *in vivo* and, therefore, broaden its effect against bacteria. (Flynn Affidavit; Van Heyningen Affidavit.)

The second prior art compound is ampicillin. Ampicillin is an oral penicillin. Ampicillin has the five member ring which is characteristic of penicillins rather than the six member ring contained in cephalosporins. This is the only difference between cephalexin and ampicillin; they have the same side chains. However, there is no evidence that side chains of penicillin and cephalosporins would parallel each other in therapeutic effect. (Tr. 292-95) The reason for adding the side chain on the penicillin nucleus was to stabilize it in acid. Cephalosporins are already stable in acid. (Flynn Affidavit; Tr. 102; 296-97.)

Another prior art reference is Stedman 7-ADCA.[5] It contains the characteristic cephalosporin nucleus with a methyl group like cephalexin at the 3 position. It suggests that side chains may be added at the 7 position. (Tr. 70-74; 99; 157; 213-14) There was no evidence indicating there was a reason specifically to try the side chain at the 7 position of cephalexin to the exclusion of a virtually limitless number of other possible combinations.

The final prior art compound upon which Premo relies is Hoover claim 7.[6] It contains a 3-methyl cephalosporin compound with a side chain at the 7 position which differs from the cephalexin side chain only in that it contains a hydroxy (OH) instead of a free amino (NH2) [*sic*] at the alpha position of the side chain. (Tr. 74; 108-09). Premo contends it would be obvious to replace the OH with NH2

5. Stedman U.S. Patent No. 3,124,576.

6. Hoover U.S. Patent No. 3,167,549.

[*sic*] upon the principle of isoterism as set forth in "Isoterism and Bio-isoterism as Guides to Structural Variations," by Virginia Schatz. [*sic*] (Tr. 112; 262) According to this principle, a chemist wanting to replace one part of a molecule with another would look for such replacements as would have roughly the same size and shape and also the same type of electronic configuration. However, on cross-examination it was brought out that the author in the same article stated that: "Two of the most unpredictable isoteres [*sic*] are the hydroxyl (OH) and amino (NH2) group. They provide examples of protagonism and antagonism to other members of this series. But more frequently they endow their respective compounds with completely different activities." (Tr. 264) Also, Hoover did not have the property of being effective orally so there was no particular reason to want to make a new compound with properties similar to Hoover.

At the conclusion of the evidentiary hearing, Premo had not yet received FDA approval to market cephalexin. It was merely stockpiling the drug in anticipation of approval. Premo is a small, closely held, family corporation with no published financial information. It was in Chapter XI reorganization as recently as 1973. (Kaufman Affidavit.) In 1978, it reported profits of $2 million. Premo may be hard pressed to respond in damages since Lilly reported gross revenue of $100 million in 1978 for cephalexin. Premo is also being sued by four other pharmaceutical companies for patent infringement. (Blackmun Deposition.) Premo has offered to set up a contingency fund of seven percent of its net sales of cephalexin.

DISCUSSION

The movant (Lilly) must show by the required degree of proof four factors as a prerequisite to obtaining a preliminary injunction against patent infringement pursuant to 35 U.S.C. § 282 (1954). These factors are: (1) the patent is valid; (2) it is infringed; (3) it is owned by the movant, *Carter-Wallace, Inc.* v. *Davis-Edwards Pharmacal Corp.*, 443, F.2d 867, 871 (2d Cir. 1971), *cert. denied,* 412 U.S. 929 (1973) (hereinafter *Carter-Wallace*); 8 *Walker on Patents* § 683 (Deller 2d ed. 1973); and (4) that irreparable harm will result if relief is not granted, *Mayview Corp* v. *Rodstein,* 480 F.2d 714, 716 (9th Cir. 1973). Where these four factors are sufficiently demonstrated, the grant of a preliminary injunction is within the discretion of the court to be exercised in light of general equitable principles regarding injunctions. *Mayview Corp.* v. *Rodstein, supra,* at 717; *Pacific Cage & Screen Co.* v. *Continental Cage Corp.*, 259 F.2d 87, 88 (9th Cir. 1958); *Zenith Labs., supra. See generally,* 8 *Walker on Patents* § 680 (Deller 2d ed. 1973).

VALIDITY

The primary issue is whether the patent is valid. Industry acquiescence is a powerful factor supporting a determination that a patent is valid, particularly in a field where competition is fierce and the patented invention has enjoyed tremendous commercial success. *Eli Lilly & Co.* v. *Generix Drug Sales,* 324 F. Supp. 715 (S.D. Fla. 1971), *aff'd,* 460 F.2d 1096 (5th Cir. 1972); *Zenith Labs., supra*;

Norwich Pharmacal Co. v. *Veterinary Corp. of America*, 296 F. Supp. 937 (M.D. Ga. 1968).[7]

Two elements are essential to a finding of acquiescence. One is a showing that the industry has a motive to challenge the patent. The best evidence of such a motive is the commercial success of the patent. The other element is that there must be an absence of infringing conduct for a substantial period of time. The greater the commercial success, the lesser the need to demonstrate a lengthy period of absence of infringing conduct, and vice versa. Acquiescence has been found in a period of five years, *McDowell* v. *Kurtz*, 77 F. 206 (3d Cir. 1896); six years, *Blount* v. *Societe Anonyme Du Filtre Chamberland Systems Pasteur*, 53 F. 98 (6th Cir. 1892); five and one-half years, *Zenith Labs., supra.*

The rationale for judicial adoption of the acquiescence standard as a substitute for technical proof of validity is "that those whose interest would lead to contest validity, have upon examination concluded that contest would be fruitless, and that that examination is some assurance of the truth." *Carter-Wallace, supra*, quoting from *Rosenberg* v. *Groov-Pin Corp.*, 81 F.2d 46, 48 (2d Cir. 1936). A substantial portion of the discussion of this issue that was contained in my prior opinion in *Zenith Labs., supra*, is pertinent here:

> Two cases illustrate factors significant to a finding of acquiescence. In *Norwich Pharmacal Co.* v. *Vet-*

7. Where there has been no showing of industry acquiescence, the standard for a preliminary injunction against infringement is an unusually high one. While the requisite showing on the merits on other than patent cases is probability of success, the party seeking to enjoin infringement ordinarily must bear the burden of demonstrating that the patent is beyond question valid and infringed. *Carter-Wallace, supra; Generix Drug Sales, supra.*

erinary Corp. of America, 296 F. Supp. 937 (M.D. Ga. 1968), the district court granted a preliminary injunction against infringement of the plaintiff's patent for furazolidone, a drug used in the poultry industry to control salmonellosis. The court found that validity had been demonstrated by acquiescence. During the 12 year life of the patent the plaintiff had given no licenses to manufacture, use or sell the drug with the exception of one implied license to sell. The court indicated that the drug industry is generally highly competitive with fierce competition arising from generic houses when any possibility of weakness appears in a commercially significant patent. Further, it found that furazolidone that would infringe the patent was available from foreign sources at low cost. Despite these facts, only a few isolated instances of infringement had occurred, and the patentee had promptly acted to defend its patent. The court gave particular weight to the conduct of the Ralston Purina Company, a poultry industry giant which used large quantities of furazolidone in its operations in both the United States and Canada. Because of the difference in scope of the plaintiff's Canadian and U.S. patents, imported furazolidone could be used in Canada without infringing the Canadian patent, while the same import would have infringed the U.S. patent. Despite Ralston Purina's concern with cost savings in an industry characterized by low profit margins, the company imported the inexpensive drug only into Canada and not into the United States. The court indicated that these facts were adequate to show acquiescence. *Id.* at 940.

In *Eli Lilly and Co.* v. *Generix Drug Sales, Inc.*, 324 F. Supp. 715 (S.D. Fla. 1971), *aff'd*, 460 F. 2d 1096 (5th Cir. 1972), a preliminary injunction issued against infringement of Lilly's patent on Darvon, the analgesic. Validity was demonstrated by evidence of acquiescence and of facts tending to disprove the defendant's attacks on the patent based on grounds of

> obviousness, anticipation and the withholding of relevant prior art from the patent examiner. As to acquiescence, the district court found that the discovery of Darvon resulted from an intensive industry search for a non-addictive analgesic with the pain-killing properties of morphine. Darvon was unique in possessing both of these qualities, and thus it met a long felt need. Darvon had exhibited great commercial success. Sales had increased to an annual rate of $65 million with aggregate wholesale sales over the life of the patent amounting to $450 million. Despite the competitive nature of the drug industry, there had been no infringement during the 16 year life of the patent with two exceptions during the 11th and 13th years. The plaintiff had immediately brought suit against the infringers and obtained consent judgments including admissions of validity. In addition, two industry members had requested licenses under the patent, demonstrating their belief in its enforceability.

460 F. Supp. at 821-22.

A preliminary injunction based primarily upon industry acquiescence was granted in *Zenith Labs., supra.* That case and this involve almost precisely the same facts. The only significant difference is that in *Zenith* the motion was for a preliminary injunction against infringement of Lilly's '656 Patent, whereas here the patent at issue is Lilly's '861 Patent. The '656 Patent covers the dense form of cephalexin monohydrate. The ability to manufacture a dense form of the chemical compound covered by the '861 Patent permits its marketing because, as explained in the *Zenith* opinion, only the dense form is sufficiently manageable to be capsulized with commercial feasibility.

Lilly's cephalexin enjoys tremendous commercial success. Keflex achieved a higher sales volume in its year of introduction, 1971, than any previously marketed phar-

maceutical product. It is the most widely prescribed oral cephalosporin in the United States today, and its annual sales in this country have increased since its introduction to a high of over $100 million in 1978. (Updated Whale Affidavit, pp. 3; 7-8.) Furthermore, the product is available from foreign sources at relatively inexpensive prices. Due to cephalexin's commercial success and availability, and considering that the drug industry is highly competitive, cephalexin is extremely attractive to other companies if they have the capability to enter the cephalexin field.

At least four major drug companies have an interest in the cephalexin field and possess the capability to make and market cephalexin in the United States. Yet, none of these companies has done so. (Lourie Deposition at 44; Sokol Deposition at 27; Updated Whale Affidavit 3-6; Supplemental Smith Affidavit 2-6.) Two of these major drug companies, Bristol-Myers Corp. and Glaxo Group Limited, have refrained from marketing cephalexin in the United States, although both companies actually manufacture and market cephalexin abroad. (Updated Whale Affidavit 3-5; Smith Affidavit 7.) Also, E.R. Squibb and Sons and SmithKline Corp. have licensing agreements with Lilly. They have paid over $1.5 million and $500,000, respectively, in royalties on the cephalexin patent. As additional consideration, they have also granted Lilly royalty-free licenses on their patents for Stedman 7-ADA and cephadrine, respectively. (Whale Affidavit; Smith Affidavit.)[8]

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8. Premo attempts to refute the conclusions concerning E.R. Squibb and Sons and SmithKline Corp. with depositions of representatives of Squibb and SmithKline which state, *inter alia,* that these companies had no interest in marketing cephalexin in the United States. This is not necessarily inconsistent with a belief the patent is valid. To the contrary, it is reasonable to infer the lack of interest in marketing cephalexin is indeed attributable to a belief that the cephalexin patent is valid. Statements alleging a lack of interest in marketing cephalexin are not sufficient to rebut the showing of acquiescence reflected by the payment of substantial royalties by Squibb and SmithKline.

Other evidence of industry acquiescence in the validity of the '861 Patent is that over 950 U.S. patents have issued in the cephalosporin field since 1958 to at least a dozen major pharmaceutical companies. (Supplemental Smith Affidavit 2-6; Whale Deposition at 50, 57, 59-60.) Lilly also has been involved in 33 patent interferences involving cephalosporins with six major pharmaceutical companies. Clearly, the pharmaceutical industry has an interest in establishing a position in the cephalosporin field. The industry has, however, refrained from manufacturing and marketing cephalexin.[9]

The only exceptions to this industry-wide acquiescence are the short-lived entry of Zenith in 1977 and the present infringement by Premo. I pointed out in *Zenith Labs., supra*:

> Where there is shown conduct sufficient to satisfy the standard for acquiescence it is presumed that members of the industry with technical expertise far greater than that of the average district court judge have examined the patent, considered such technical arguments as Zenith poses here and decided them in the patentee's favor. It is said the burden of validity is ameliorated where there is acquiescence. *Eli Lilly and Co.* v. *Gen-*

9. Another indicia of patent validity is that the subject of the patent has satisfied a long-felt need. *Graham* v. *John Deere Co.*, 383 U.S. 1, 17-18 (1963). Cephalexin satisfies a need felt ever since the introduction of penicillin. Infections resistant to that drug plagued the medical profession, since penicillin is effective only against gram-positive organisms. The question of finding additional antibiotic medications became extremely important. (Tr. 113-14) The search for a safe orally administered antibiotic effective against a broad spectrum of both gram-positive and gram-negative bacteria has largely been satisfied with the advent of Lilly's Keflex. The value of this medication hardly can be overstated. It is the first oral medication of choice where both gram-positive and gram-negative therapy is sought. Until Keflex was marketed, no such medication existed.

> *erix Drug Sales, Inc., supra,* at 1099. In light of the presumption underlying the acquiescence doctrine, I interpret this statement to mean that the burden on the district court to treat fully and resolve with certainty technical attacks on the patent is also substantially reduced where acquiescence is shown. If the rule is otherwise, the patentee must always be a second class citizen before the courts on an application for a preliminary injunction of infringement. The reason for his lowly status is not necessarily the invalidity of his patent, but the lack of technical training in the court necessary to resolve substantive arguments made by even the most egregious infringer.

460 F. Supp. at 823-24.

Premo contends that it would be in the public interest to deny Lilly an injunction at this time because Lilly has had sufficient enjoyment of its monopoly and denial of an injunction would open the market to a less expensive generic cephalexin. Insofar as this argument is directed to the length of the patent monopoly, it is not for the federal courts, but for Congress. As I said in *Zenith Labs., supra,* Lilly has well served the public interest in inventing and marketing cephalexin. 460 F. Supp. at 826. The purpose of the Patent Act is to encourage exactly what Lilly has done. It has invested millions of dollars in a new drug of dramatic and beneficial properties. That new drug will one day be in the public domain. If strike suits by generic houses when a new drug achieves vast commercial success cannot be met with preliminary relief, but must be left to wend their way to final judgment on crowded dockets, then

such invention will be discouraged and the purpose of the Patent Act will be frustrated.[10]

While the holding of this case is based substantially upon the presumed analyses of this patent conducted by persons with sophistication in these areas far greater than my own, nonetheless, my own independent evaluation of the statutory challenge also supports validity.

Only the third statutory criteria for the grant of a patent, section 103 "non-obviousness," is seriously in dispute.[11] The Supreme Court in *Graham* v. *John Deere Co.*, 383 U.S. 1 (1966) set forth the law relating to obviousness under 35 U.S.C. § 103 as follows:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.

10. There is no danger that the '656 and '861 Patents give Lilly the power to become a predatory monopolist. At a hearing on April 3, 1979, I received permission of the parties to consider Vol. 20, No. 1 of The Medical Letter, Jan. 13, 1978 published by The Medical Letter, Inc., New Rochelle, N.Y. (Tr. 21-22) This publication discusses the choice of antimicrobial drugs. It lists the most widely encountered gram-positive and gram-negative bacteria and lists for each the drug of first choice and alternative drugs. In no case is a cephalosporin a drug of first choice, although in many instances cephalosporins are listed among the alternative therapy. It thus appears that there is nothing Keflex can do that another available drug cannot do as well or better.

11. 35 U.S.C. § 103.

> Conditions for patentability; non-obvious subject matter.
>
> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> Against this background, the obviousness or nonobviousness of the subject matter is determined.

385 U.S. at 17.

There are conflicting views as to the factors that may be considered when analyzing a challenge on obviousness grounds to a patent on a chemical compound. One view asserts that structural obviousness of the claimed compound from the prior art reference is an absolute bar to a patent. A difference in chemical properties is irrelevant in determining obviousness and is only applicable in determining utility under 35 U.S.C. § 101. *Carter-Wallace, Inc.* v. *Davis-Edwards Pharmacal Corp.*, 341 F. Supp. 1303 (E.D.N.Y.), *aff'd on other grounds*, 443 F.2d 867 (2d Cir. 1971), *cert. denied*, 412 U.S. 929 (1973). *See* n. 12, *infra*.

The other view rejects this contention and holds that a new and unexpected property may impart unobviousness to an otherwise structurally obvious compound. *In re May*, 574 F.2d 1082 (C.C.P.A. 1978); *Commr's of Patents* v. *Deutsche Gold-und-Silber*, 397 F.2d 656 (D.C. Cir. 1968); *In re Papesch*, 315 F.2d 381 (C.C.P.A. 1963). Title 35 U.S.C. § 103 provides that an invention is obvious and unpatentable only if "the subject matter *as a whole* would have been obvious at the time the invention was made" to one skilled in the art. (Emphasis added). It is a reasonable statutory interpretation to include the properties of a chemical invention when determining whether the compound *as a whole* is obvious.

The leading case following the unexpected property standard is *In re Papesch, supra*. There, the applicant claimed compounds possessing potent anti-inflammatory activity. The Patent Office rejected the claims as obvious

in light of a prior art compound having a chemical structure which was identical to the claimed compound except for a methyl rather than an ethyl or butyl substituent at one position. The applicant filed an affidavit demonstrating that the reference compound, unlike the claimed compound, displayed no anti-inflammatory activity, but the Patent Office held that unexpected utility would not render a structurally obvious compound unobvious. The Court of Customs and Patent Appeals reversed, and held that a compound structurally similar to a prior art compound may nevertheless be unobvious and patentable when evidence shows it to possess unexpected properties.

In *Deutsche Gold-und-Silber, supra,* the Court of Appeals for the D.C. Circuit, speaking through Judge (now Chief Justice) Burger, followed *Papesch* and held that a structurally similar chemical compound may nevertheless be patentable when it possesses novel or superior properties. The court stated:

> The sound reasoning of the *Papesch* case has been unanimously and repeatedly reaffirmed by the Court of Customs and Patent Appeals. Doubtless we must agree with admonitions against deciding questions of chemical obviousness on the basis of structure alone.
>
> * * *
>
> A second factor, to which we have already alluded, is the rare occurrence in finding a completely new compound whose molecular arrangements cannot be predicted, at least on paper. If we are to accept a determination of structural obviousness which cannot be rebutted by evidence of chemical, pharmaceutical, or biological properties, *few pharmaceutical compounds will be patented, and the incentive aspect of*

> *the patent system,* which is basic, *will be lost* from an important area.

397 F.2d at 662-63. (Emphasis added.)[12]

Structural obviousness generally arises because the claimed compound is a homolog, analog, or isomer. Yet, no inference can be drawn that structural similarity of a compound implies similar properties. In *In re May, supra,* the Court of Customs and Patent Appeals explained that structural similarity of chemical compounds is relevant only insofar as it gives rise to a presumption that compounds of similar structures will exhibit similar properties. The

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12. District Judge Dooling in *Carter-Wallace,* in response to the problem that it is a rare occurrence to find a novel compound, stated:

> It may be that few claims on new chemical compositions will issue if what is readily synthesized by known methods is denied patentability as a new composition of matter because it is obvious in the art of chemical synthesis even though it evinces unanticipated "properties" or utilities so that it was—antecedently—an obvious choice for screening and testing in a search for such "properties" or utilities; it is said that today the art of chemical synthesis is capable of producing new compounds almost to formulary and structural specification. That tribute to the level of skill prevalent in organic chemistry simply signifies that the front of patentable chemical innovation is far out, not that it is non-existent, or that the nearer tasks that have become ready and obvious of solution must be protected in their unexpectedly beneficial results by patents on what is not the innovative aspect of the effort.

Carter-Wallace, Inc. v. *Davis-Edwards Pharmacal Corp.,* 341 F. Supp. at 1340 (E.D.N.Y.), *aff'd,* 443 F.2d 867 (2d Cir. 1971).

However, recently, the Court of Appeals for the Fifth Circuit, in *Generix Drug Sales, supra,* noted:

> A limitation to "use" or process patentability, based solely on the existence of prior chemical formulations, would not accord with the basic constitutional power being exercised by the Congress to promote science and the useful arts. Such a niggardly patent reward for costly and painstaking research would discourage both the inspiration-perspiration process of the laboratory and the incentive to publicly disclose products of value to mankind.

460 F.2d at 1103.

court indicated that such a presumption may be rebutted not only by showing a difference in actual properties between the claimed compound and prior art compounds, but alternatively by showing that a substantial degree of unpredictability exists in the prior art area.

Here, if the contention of obviousness were limited to a comparison of the structure of cephalexin to that of its analogs, then there is some convincing evidence that cephalexin was structurally obvious. A prior art compound is cephaloglycin. Cephaloglycin consists of the 7-ACA cephalosporin nucleus with the naturally occurring acetoxymethyl group at the 3 position and the same alpha-aminobenzyl side chain as cephalexin at the 7 position. The only difference between cephalexin and cephaloglycin is that cephalexin has a methyl group at the 3 position whereas cephaloglycin has an acetoxymethyl group at the 3 position. Cephaloglycin, unlike most cephalosporins, was inactive against gram-negative bacteria. The reason for this was that the acetyl portion of the acetoxymethyl group at the 3 position was removed (deacetylated) *in vivo*. Compounds containing only a methyl group cannot, by definition, undergo deacetylation. Therefore, the fact that Lilly chose the methyl group was an obvious modification of cephaloglycin.[13]

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13. Premo relies on several other prior art compounds in order to show chemical obviousness. These are Stedman claim 7-ADCA (cephalosporin nucleus with a methyl group rather than an acetoxymethyl group at the 3 position); ampicillin (oral penicillin); and the Hoover claim 7 (a 3-methyl cephalosporin compound with a side chain at the 7 position which differs from the cephalexin side chain in that it contains a hydroxy group instead of a free amino group at the alpha position of the side chain).

Concededly, two dimensional diagrams of cephalexin and these prior art compounds may visually resemble one another and one

(footnote continued on next page)

What was indisputedly non-obvious was that cephalexin would be 100% absorbed when administered orally. This property was totally unexpected considering cephaloglycin was absorbed to the extent of about 20%. It is not possible to predict whether a compound will be effectively absorbed because biochemists do not understand the mechanism of absorption. (Tr. 301) If this court follows the *Papesch* case and its progeny, then cephalexin's unexpected property may confer non-obviousness to an otherwise structurally obvious compound.

This court rejects Judge Dooling's analysis in *Carter-Wallace, see* n. 12, *supra,* and follows *Papesch* because the latter more accurately reflects the purpose for research

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skilled in the art could make cephalexin from these compounds if specifically asked to do so. However, in view of the enormous number of possible substituents which could be added to different positions on the cephalosporin nucleus and the inability of those skilled in the art to predict what properties or utility the resulting compounds would have, it is necessary for Premo to show that the prior art would have led those skilled in the art specifically to conceive and prepare cephalexin as a solution to the search for an orally effective antibiotic. In other words, there had to be a reason other than academic or theoretical for the structural change. *In re Stemniski,* 444 F.2d 581 (C.C.P.A. 1971). In the present case, the changes were performed in the routine of experimentation. Premo's own expert, Dr. Bose, pointed out that "millions" of side chains could be added to the cephalosporin nucleus, (Tr. 244), and that hundreds of thousands of side chains are known in the penicillin art. (Tr. 43; 190-93). Similarly, both Dr. Bose and Lilly's expert, Professor Abraham, agreed, and all the other record evidence indicates, that slight differences in chemical structure could result in marked differences in properties and that one skilled in the antibiotic or medicinal chemistry art could not predict what those properties would be. (Tr. 44, 138, 198, 202, 264, 280, 283, 292-93, 300-01, 411-12; Flynn Deposition 13-14.)

Premo contends that the fact that the side chains were added merely in the routine of experimentation lends weight to a finding of obviousness. This is not consistent with section 103 which specifically states in pertinent part: "Patentability shall not be negatived by the manner in which the invention was made."

and development in the pharmaceutical industry. The drug industry invests millions of dollars to invent compounds with beneficial properties. If the patent system insists that a structure must be novel to be patentable, then the law inhibits the search for cures for disease. Such insistance [*sic*] would undoubtedly increase the cost of research and development because the scientist would be forced to work within the fiction that the compound must be novel. Moreover, this fiction might discourage companies from investing in the testing of structurally obvious compounds that may have beneficial properties. There is no logical reason to limit patents to novel structures. The patent system should encourage the research and development of chemical compounds with beneficial properties, not merely novel structures.

While both parties concede that cephalexin's unexpected property (100% gut absorption) is non-obvious, the defendant contends that Lilly should not have the benefit of this property in analyzing non-obviousness because Lilly did not adequately disclose cephalexin's oral property.

In support of its position, defendant cites *Carter-Wallace, Inc.* v. *Otte,* 474 F.2d 529 (2d Cir. 1972), *cert. denied,* 412 U.S. 929 (1973). Carter-Wallace obtained a patent on the drug product meprobomate and sought to rely on its effectiveness as a tranquilizer as an unexpected property supporting its patentability, notwithstanding its structural obviousness. The patent specifications, however, disclosed that meprobomate was useful as an anticonvulsant and muscle relaxant, and made no mention of its separate utility as a tranquilizer. The court concluded that Carter-Wallace could not rely on the unexpected tranquilizing properties of meprobomate because in order to

realize the advantage of those properties, it was necessary to use the compound in a manner not disclosed in the patent application. The court stated:

> Although the primary purposes of requiring this degree of disclosure [under 35 U.S.C. § 112] may be to insure that the invention can be reconstructed and that the boundary separating legitimate experimentation from infringement is clear . . . both of which are fulfilled here, similar reasoning justifies a high standard of disclosure when a property of an obvious chemical compound is relied upon to establish patentability under the *Papesch* doctrine. In the absence of such disclosure the public will not obtain the benefit of the particular use which justified the grant of the patent. Applying this standard, we conclude that nothing in the specifications of the CIP application would have led the typical skilled worker in the art to use meprobomate as tranquilizer.

474 F.2d at 542.

The facts of *Carter-Wallace, Inc.* v. *Otte* are distinguishable from this case. Here, the abstract to the patent, which was added via amendment to the application, states that cephalexin is "especially of interest for its use as an antibiotic when administered by the oral route." This statement informs one skilled in the art (as well as the public generally) of what one needs to know to obtain all the benefits of the unexpected properties of cephalexin. The utility of cephalexin is that of an oral antibiotic. The advantage of its high oral effectiveness attributable to its 100% absorption rate inherently flows from its utility, and the public thus obtains the benefit of its properties.

INFRINGEMENT AND OWNERSHIP

The requirements that Premo infringed and Lilly owns Patent '861 are not in dispute.

SUMMARY ON THE ISSUE OF VALIDITY

For two broad reasons it is my determination that Lilly has shown the validity of its '861 Patent to a sufficiently high degree of probability to entitle it to a preliminary injunction. First, it has shown validity by the collateral standards of patentability—significant commercial success, industry acquiescence and satisfaction of a long-felt need. Second, and alternatively, an overview of the prior art persuades me that the '861 Patent was not obvious under what I believe should be, and is, the prevailing legal standard.

IRREPARABLE HARM

The fourth requirement for the issuance of a preliminary injunction is a showing of irreparable harm. This court in *Zenith Labs., supra,* stated:

> The availability of a legal remedy in the form of damages has not always precluded the grant of a preliminary injunction. *Hilditch* v. *American Bumper Corp.,* 15 F.2d 451, 452 (E.D.N.Y. 1926). In my view, where the showing on validity is very strong, invasion of the monopoly rights protected by the patent laws should be sufficient irreparable harm without a showing that the infringer is financially irresponsible. *Contra, Nuclear-Chicago Corp.* v. *Nuclear Data, Inc.,* 465 F.2d 428 (7th Cir. 1972). Here the potential market diversion, the invasion of Lilly's right to exploit its patent up until now exercised solely by Lilly, and the taking advantage of the research and promotional activities performed by Lilly before the expiration of patent protection should be sufficient to carry the burden on irreparable harm. Indeed, in *Eli Lilly and Co.* v. *Generix Drug Sales, Inc., supra,* 324 F. Supp. 725, in

> granting a preliminary injunction the district court relied on such factors, making no finding of financial irresponsibility. The district court subsequently set the case down *sua sponte* for a hearing, and finding no triable issue of fact, entered a permanent injunction. *Id.*, 460 F.2d 1099. The Fifth Circuit apparently determined that a temporary injunction might be issued without financial irresponsibility, for it affirmed the grant of the preliminary injunction while reversing the grant of a permanent one.

460 F. Supp. at 825.

The strong showing of patent validity coupled with Premo's conceded willful infringement of Lilly's patent is sufficient to carry the burden on irreparable harm.

While Premo's financial condition is better than Zenith's, it still may be hard pressed to respond in damages. Premo was in Chapter XI reorganization in 1973 and reported profits of $2 million in 1978. Premo is also being sued by four other pharmamceutical companies for patent infringement. *See* Blackman Dep. of December 12, 1978 at 30-31. Considering Lilly's sales for cephalexin were $100 million for 1978, damages could very conceivably run beyond Premo's ability to pay them.

PUBLIC INTEREST AND THE BALANCE OF THE EQUITIES

In *Zenith Labs., supra,* this court stated:

> While Zenith does provide drugs at low cost, Lilly has served the public to a greater degree by its initial development and testing of Keflex and its continuing program of testing to ensure the drug's efficacy and safety. As to the relative inconveniences, the grant of this motion would halt Zenith's processing of cepha-

> lexin monohydrate, but the impact will be considerably less than if Zenith itself manufactured the drug. If the motion is denied, Zenith will continue to cut into Lilly's profits which appear to be protected by a valid patent. In addition, it is likely that other generic houses will enter the market, as is the pattern in the drug industry where a commercially successful patent is challenged. Lilly would be drawn into further litigation to defend its patent, and the loss of profits resulting from the increased competition would result in a reduction of funds available for testing and research and development. Under these circumstances, the balance of the equities is tipped in Lilly's favor.

460 F. Supp. at 826.

CONCLUSION

For the foregoing reasons, this court holds that Lilly is entitled to a preliminary injunction against infringement of its '861 Patent. Lilly will have to post an injunction bond pursuant to Fed. R. Civ. P. 65(c). If the parties cannot agree, the terms of the bond will be determined after hearing. An order in accord with this decision should be prepared and submitted by Lilly within 10 days with consent as to form, if possible.[14]

DATED: July 13, 1979.

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14. Premo raises the specious argument that Morin and Jackson are not the sole inventors of the patent and, therefore, the patent is void. Premo alleges that the scientist who subsequently discovered the extent of absorption must be listed as one of the inventors. This argument is without merit. As *In re Papesch, supra,* dictates, the inventor of the compound itself receives a patent on that compound which necessarily includes its inherent properties.

APPENDIX C

Judgment of the United States Court of Appeals for the Third Circuit Entered on August 4, 1980

UNITED STATES COURT OF APPEALS

FOR THE THIRD CIRCUIT

No. 79-1954

ELI LILLY AND COMPANY,

vs.

PREMO PHARMACEUTICAL LABORATORIES, INC.,
Federal Pharmacal, Inc.,
Seymour N. Blackman, Steven Blackman,
John Blackman,

Appellants,

vs.

Richard D. Wood, C. Harvey Bradley, Jr.,
Earl B. Herr, Jr., Cornelius W. Pettinga,
Eugene L. Step and Arthur R. Whale,

Additional defendants on the Counterclaim.

(D. C. Civil No. 78-2589)

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE ——— DISTRICT OF NEW JERSEY

Present: ADAMS, VAN DUSEN and GARTH, *Circuit Judges*

JUDGMENT

This cause came on to be heard on the record from the United States District Court for the ——— District of New Jersey and was argued by counsel on February 14, 1980.

On consideration whereof, it is now here ordered and adjudged by this Court that the judgment of the said District Court, filed July 24, 1979, be, and the same is hereby affirmed. Costs to be taxed against appellants.

ATTEST:

/s/ THOMAS F. QUINN
Clerk

July 11, 1980

Certified as a true copy and issued in lieu
of a formal mandate on August 4, 1980.

Test: SALLY MRVOS

Clerk, United States Court of Appeals
for the Third Circuit

APPENDIX D

Preliminary Injunction Order of the United States District Court for The District of New Jersey Entered on July 24, 1979

IN THE

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

Civil Action No. 78-2589 (HCM)

ELI LILLY AND COMPANY,

Plaintiff,

v.

PREMO PHARMACEUTICAL LABORATORIES, INC., *et al.*,

Defendants.

For the reasons stated in the Opinion of this Court dated July 13, 1979, it is this 24 day of July, 1979, ORDERED:

1. Defendants Premo Pharmaceutical Laboratories, Inc., Federal Pharmacal, Inc., Seymour N. Blackman, Steven Blackman, John Blackman, their subsidiaries, affiliates, successors, assigns, directors, officers, agents, servants, employees and attorneys, and any person or entity in active concert or participation with them, or any of them, who

receives actual notice or this Order by personal service or otherwise, including any such distributors, suppliers, and hospital and retail pharmacies, who are in active concert or participation with them, be and they are preliminarily enjoined, until further order of this Court, from directly or indirectly infringing or inducing infringement of Claims 12 and 16 of United States Patent No. 3,507,861 owned by plaintiff Eli Lilly and Company, by the manufacture, use, sale, offering for sale, or promoting or inducing the sale in the United States, its territories or possessions, of cephalexin as described in those claims.

2. This injunctive order shall become effective upon posting by plaintiff Eli Lilly and Company of a Bond or other security in the sum of ONE MILLION DOLLARS ($1,000,000) to secure the payment of such costs and damages as may be incurred or suffered by defendants in the event that this injunctive order shall be subsequently dissolved by order of Court upon a finding that defendants were wrongfully enjoined.

/s/ H. CURTIS MEANOR

U.S.D.J.

APPENDIX E

Statutes

Title 35 of United States Code §§ 101, 102(f), 103, 111, 112, 116, 120, 132, 154

§ 101. Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

§ 102. Conditions for patentability; novelty and loss of right to patent

A person shall be entitled to a patent unless—

• • •

(f) he did not himself invent the subject matter sought to be patented . . .

• • •

§ 103. Conditions for patentability; non-obvious subject matter

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

§ 111. Application for patent

Application for patent shall be made by the inventor, except as otherwise provided in this title, in writing to the Commissioner. Such application shall include: (1) a specification as prescribed by section 112 of this title; (2) a drawing as prescribed by section 113 of this title; and (3) an oath by the applicant as prescribed by section 115 of this title. The application must be signed by the applicant and accompanied by the fee required by law.

§ 112. Specification

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

* * *

§ 116. Joint inventors

When an invention is made by two or more persons jointly, they shall apply for patent jointly and each sign the application and make the required oath, except as otherwise provided in this title.

If a joint inventor refuses to join in an application for patent or cannot be found or reached after diligent effort, the application may be made by the other inventor on behalf of himself and the omitted inventor. The Commissioner,

on proof of the pertinent facts and after such notice to the omitted inventor as he prescribes, may grant a patent to the inventor making the application, subject to the same rights which the omitted inventor would have had if he had been joined. The omitted inventor may subsequently join in the application.

Whenever a person is joined in an application for patent as joint inventor through error, or a joint inventor is not included in an application through error and such error arose without any deceptive intention on his part, the Commissioner may permit the application to be amended accordingly, under such terms as he prescribes.

§ 120. Benefit of earlier filing date in the United States

An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, by the same inventor shall have the same effect, as such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

§ 132. Notice of rejection; reexamination

Whenever, on examination, any claim for a patent is rejected, or any objection or requirement made, the Commissioner shall notify the applicant thereof, stating the reasons for such rejection, or objection or requirement, together with such information and references as may be useful in judging of the propriety of continuing the prose-

cution of his application; and if after receiving such notice, the applicant persists in his claim for a patent, with or without amendment, the application shall be reexamined. No amendment shall introduce new matter into the disclosure of the invention.

§ 154. Contents and term of patent

Every patent shall contain a short title of the invention and a grant to the patentee, his heirs or assigns, for the term of seventeen years, subject to the payment of issue fees as provided for in this title, of the right to exclude others from making, using, or selling the invention throughout the United States, referring to the specification for the particulars thereof. A copy of the specification and drawings shall be annexed to the patent and be a part thereof.

Rules

Rule 72(b) of the Rules of Practice in the United States Patent Office (37 C.F.R. § 1.72(b))

§ 1.72 Title and abstract.

* * *

(b) A brief abstract of the technical disclosure in the specification must be set forth on a separate sheet, preferably following the claims under the heading "Abstract of the Disclosure." The purpose of the abstract is to enable the Patent and Trademark Office and the public generally to determine quickly from a cursory inspection the nature and gist of the technical disclosure. The abstract shall not be used for interpreting the scope of the claims.

APPENDIX F

United States Letter Patent No. 3,507,861

United States Patent Office 3,507,861 Patented Apr. 21, 1970

3,507,861
CERTAIN 3-METHYL-CEPHALOSPORIN COMPOUNDS

Robert B. Morin and Billy G. Jackson, Indianapolis, Ind., assignors to Eli Lilly and Company, Indianapolis, Ind., a corporation of Indiana

No Drawing. Continuation-in-part of application Ser. No. 213,588, July 31, 1962. This application Sept. 14, 1966, Ser. No. 579,222

Int. Cl. C07d 99/24

U.S. Cl. 260—243 16 Claims

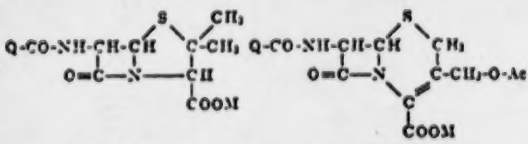
ABSTRACT OF THE DISCLOSURE

Certain 3-methyl-cephalosporin compounds useful as antibiotics, e.g., 3-methyl-7-(D-α-aminophenylacetamido)-Δ^3-cephem-4-carboxylic acid, now known generically as cephalexin, especially of interest for its use as an antibiotic when administered by the oral route.

This application is a continuation-in-part of our application Ser. No. 213,588, filed July 31, 1962, now Patent No. 3,275,626.

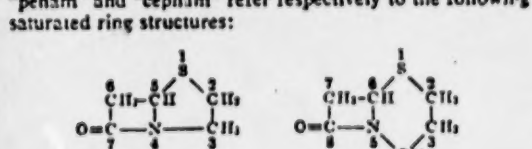
The present invention relates to antibiotic substances. More particularly it relates to certain penicillin-derived antibiotic substances and to novel methods for their production.

The first of the antibiotics to be discovered were the penicillins, which contain the penam nucleus, a thiazolidine ring with a fused β-lactam. A more recent discovery is the cephalosporins, which contain the Δ^3-cephem nucleus, a dihydrothiazine ring with a fused β-lactam. These two classes of antibiotics are thus somewhat related in structure, as will be seen from the following general structural formuals:



Penicillins Cephalosporins

wherein Q represents essentially any organic radical, as exemplified by hundreds of examples in the prior art, and M represents a pharmaceutically acceptable cation. The penam nomenclature for the penicillins is described by Sheehan, Henery-Logan, and Johnson in the J. Am. Chem. Soc., 75, 3293, footnote 2 (1953), and has been adapted to the cephalosporins by Morin, Jackson, Flynn, and Roeske in the J. Am. Chem. Soc., 84, 3400 (1962). In accordance with these systems of nomenclature, "penam" and "cepham" refer respectively to the following saturated ring structures:



Penam Cepham

while "penam" and "cephem" refer to the same ring structure with a double bond, the position of which is indicated by a prefixed "Δ" with superscript denoting the carbon atom of lowest number to which the double bond is connected.

While both the penicillins and the cephalosporins have been remarkably effective in the treatment of a variety of

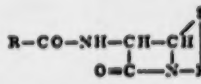
infections, there is a continuing need for different and improved antibiotics. There has also been a need for a simple and economical method for synthesizing the cehalosporin compounds from available starting materials.

One object of the present invention is to prepare novel antibiotic substances.

Another object is to prepare modified cephalosporins.

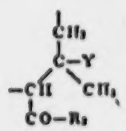
Other objects of the invention and its advantages over the prior art will be apparent from the following description, operating examples, and claims.

In one aspect, the present invention affords a novel class of compounds having the following structure:

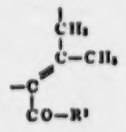


(I)

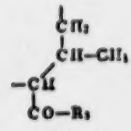
where R is an organic radical as hereinafter defined, and R^1 has a structure represented by one of the following formulas:



(Ia)



(Ib)



(Ic)

where R^3, when linked directly to the molecule, is $—NH_2$, —NH—(C_1–C_4 alkyl), or —N=di(C_1–C_4 alkyl);

where R^2, when linked to the molecule through —O—, is hydrogen, a pharmaceutically acceptable cation, C_1–C_4 alkyl, C_4–C_7 cycloalkyl, or phenyl;

and where Y is C_2–C_4 alkanoyloxy or C_1–C_4 alkoxy.

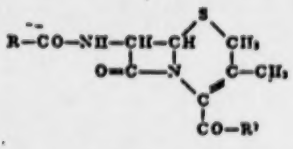
In the above formulas, R^3, when linked directly to the molecule to form amides, may be exemplified by

$CH_3NH—$, $C_2H_5NH—$, $C_4H_9NH—$, $(CH_3)_2N—$,

$(C_2H_5)_2N—$, and $CH_3(C_2H_5)N—$. When linked to the molecule through an oxygen atom to form carboxylic acids, salts, and esters, R^3 may be exemplified by hydrogen; sodium, potassium, and ammonium; methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, isobutyl, and tert.-butyl; cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl; and phenyl, which may be in substituted form, e.g., chlorophenyl, bromophenyl, trichloromethylphenyl, nitrophenyl, methoxyphenyl, tolyl, and the like, the substituents being in the o-, m-, or p-position, and further substitution with these and other substituents being permitted.

Y may be exemplified by acetoxy, propionoxy, butyroxy, methoxy, ethoxy, propoxy, butoxy, and the like.

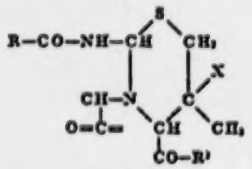
Thus, among the compounds of the invention are the cephem compounds of the following structure:



(II)

and the dihydro derivatives thereof, wherein R and R^2 are as defined elsewhere herein.

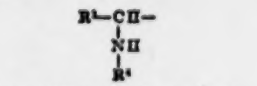
Also included are cepham compounds of the following structure:



(III)

wherein R, R^2, and Y are as defined elsewhere herein.

The side chain R of the penicillin starting material (and thus of the cephalosporin product) can be chosen from a wide variety of organic radicals which are stable under the reaction conditions and which yield products of improved properties. Suitably R has the structure



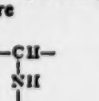
where

R^2 is phenyl, or phen(C_1–C_4)alkyl;

R^4 is hydrogen or methyl; and

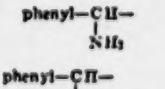
R^5 is C_1–C_8 alkyl or a member of the same group as R^2, the various rings having optionally one or more substituents such as halo, alkyl, nitro, amino, acyl, trifluoromethyl, alkoxy, alkylmercapto, and the like.

Where R has the structure



it will be apparent that the product can exist in the form of the inner salt or as a salt of a pharmaceutically acceptable acid, or the like and such salt forms are considered to lie within the scope of the invention as claimed.

Thus, R may be chosen from the following types of structures:



phenyl—O—CH_2—
phenyl—S—CH_2—
phenalkyl—O—CH_2—
phenalkyl—S—CH_2—
(C_1–C_8 alkyl)—O—CH_2—
(C_1–C_8 alkyl)—S—CH_2—

Illustrative penicillins (and cephalosporin products) include, but are not limited to, the following, referring only to the R group thereof, attached through —CO—NH— to the antibiotic nucleus:

Phenoxymethyl
Benzyloxymethyl
Phenethoxymethyl
n-Hexyloxymethyl
Ethylmercaptomethyl
n-Butylmercaptomethyl
Phenylmercaptomethyl
Benzylmercaptomethyl
Phenethylmercaptomethyl
α-Aminobenzyl
α-(Methylamino)benzyl.

The penicillins can be employed in the form of the free acids; the sodium, potassium, amine, or other salts; the methyl, ethyl, n-butyl, or other esters; or the amide, the N-methylamide, the N,N-diethylamide, or other amides, the choice depending to some extent upon the desired end product, since the course of the reaction is influenced by the structure of the penicillin at the carboxyl group, as pointed out below.

Further illustrative examples of the products of the present invention include the following, but it is to be understood that the invention is not limited thereto:

3-propionoxy-3-methyl-7-phenylmercaptoacetamidocepham-4-carboxylic acid sodium salt
7-(p-fluorobenzylmercaptoacetamido)-3-methyl-Δ^3-cephem-4-carboxylic acid potassium salt
7-phenethylmercaptoacetamido-3-methyl-Δ^3-cephem-4-carboxylic acid potassium salt
3-methyl-7-n-butylmercaptoacetamidocepham-4-carboxylic acid butyl ester

In one method for preparing the compounds of the present invention, a penicillin having a 6-acylamido substituent group as desired is first subjected to treatment with an oxidizing agent such as metaperiodic acid to produce the corresponding sulfoxide. The latter is then heated to elevated temperature in the presence of an acidic substance such as acetic anhydride or sulfuric acid or the like, thereby producing the desired substance.

The acid substance can be employed in catalytic proportions, of the order of 1 to 10 percent by weight of the penicillin sulfoxide, where the acid substance does not supply an element of the desired product. The catalytic reaction is thus feasible in the production of the compounds of the invention which do not include the radical Y. When the desired product does include the radical Y, the acid substance must afford the radical in equimolar proportion to the penicillin sulfoxide.

No solvent or other liquid medium is necessary for the reaction, but is desirable in order to facilitate heat transfer and to moderate the reaction. Any organic liquid can be used as the reaction medium so long as it is substantially inert to the other reactants under the conditions employed. A preferred solvent and acid reactant combined in acetic anhydride. The reaction temperature should lie in the range of about 100 to about 175° C., preferably about 125 to about 150° C. The conversion is generally found to reach a substantial level after as little as 5 minutes, and is ordinarily complete in less than one hour. The reaction time should be kept as short as possible in order to minimize the formation of undesirable by-products.

After completion of the reaction, the reaction mixture is cooled, and the solvent, if any, is stripped off at reduced pressure. The residue obtained thereby is separated into its components by any convenient method, such as chromatography over silica gel or the like, employing a ketonic solvent for the elution. Other adsorbent solids may be employed as desired, such as silica-alumina, cellulose, Florisil, or the like. For the solvent, methyl isobutyl ketone, methyl ethyl ketone, or acetone can be employed, diluted to some extent with a nonpolar solvent such as hexane, cyclohexane, or benzene, and preferably contain-

ing at least some proportion of water, up to the saturation level. The crude substance is first dissolved in an organic solvent such as the eluting solvent to be used thereafter, which solution is applied to the chromatographic column. Elution is then carried out, the eluate fractions being checked by thin-layer chromatography to identify the products in the successive fractions. The appropriate fractions are combined and are further treated to isolate the individual products, suitably by crystallization.

The free acids and salts of the products of the invention can be obtained from the esters or amides by selective hydrolysis in a conventional manner, or from suitable esters by catalytic hydrogenolysis.

Generally speaking, it is desirable to treat the penicillin sulfoxide in the form of an ester or an amide, in order to avoid loss of the carboxyl group in the 4-position.

In the new compounds provided by the present invention, the β-lactam has greater chemical and penicillinase stability than the compounds of the prior art. The acids and salts exhibit the ability in greater or lesser degree to destroy or inhibit the growth of many microorganisms, among which are the Staphylococci, the Streptococci, and the Bacilli. Numerous uses for the compounds will thus be apparent from the art; e.g., as topical sterilants. The esters and amides are useful as intermediates in the production of the acids and salts. The products of the invention are additionally useful as intermediates for the synthesis of still newer antibiotic substances, in particular certain derivatives of cephalosporin C. The unsaturated compounds can be reacted, for example, with oxidizing agents, carboxylating agents, halogenating agents, and other substances to produce derivatives of modified or enhanced effectiveness. They can be hydrogenated in the presence of palladium catalysts to produce the saturated compounds. Modified cephalosporins can be obtained by oxidizing cephem compounds by known techniques for oxidizing allylic carbon atoms, employing, for example, N-bromosuccinimide, lead tetraacetate, or selenium dioxide.

The structures of the compounds of the present invention have been proved by way of their infrared, ultraviolet, and nuclear magnetic resonance spectra. They are conveniently analyzed by the method of Ford, Analytical Chemistry, 19, 1004 (1946), which is based upon the quantitative determination of the β-lactam moiety of the molecule via reaction with hydroxylamine. Their antibiotic potencies are readily determined against a standard organism such as *Staphylococcus aureus* 209 P by appropriate modifications of the paper disc plate methods of Higgens et al., Antibiotics & Chemotherapy, 3, 50–54 (1953) and Loo et al., Journal of Bacteriology, 50, 701–709 (1945).

The invention will be more fully understood from the following operating examples:

Example 1

Penicillin V sulfoxide.—Sodium metaperiodate (8.0 g.) was added in one portion with stirring to a solution of 15.5 g. of penicillin V potassium salt in 300 ml. of water at room temperature, and stirring was continued while occasional starch-iodide tests for active oxygen were made. After 45 minutes the test became negative. The mixture was then diluted with 100 ml. of water and acidified to pH 2.3 with dilute hydrochloric acid. Penicillin V sulfoxide was precipitated thereby as the free acid, and was collected and recrystallized from aqueous methanol (1:2). The product weighed 12.3 g. and melted at 163–164° C. with decomposition.

Penicillin V sulfoxide methyl ester.—Three grams of penicillin V sulfoxide in the form of the free acid were suspended in 30 ml. of ethyl acetate. The suspension was stirred at room temperature, and to it was added a dilute solution of diazomethane in ethyl ether until the yellow color persisted. The mixture was then evaporated to dryness at reduced pressure and the residue was recrystallized from aqueous methanol. The product, weighing 2.5 g., was the methyl ester of penicillin V sulfoxide, melting at 120–122° C. Further recrystallization yielded an analytical sample melting at 121.5–122.5° C., $[\alpha]_D = +200.0$.

Acetoxymethylpenam and acetoxycepham derivative.—A solution of 500 mg. of penicillin V sulfoxide methyl ester in 35 ml. of acetic anhydride was heated at reflux for one-half hour and then evaporated to dryness at reduced pressure. The oily residue obtained thereby was taken up in ethyl acetate and the solution was washed successively with cold dilute aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution. The washed solution was dried over sodium sulfate and evaporated to dryness at reduced pressure. The amorphous product (530 mg.) obtained thereby was chromatographed through a silicic acid column, using a mixture of cyclohexane and methyl isopropyl ketone (4:1) saturated with water as the eluting solvent. The eluate was collected in 7-ml. fractions at 20-minute intervals, which were analyzed by thin-layer chromatography and suitably combined for product isolation.

Fractions 75–88, 195 mg., constituted the penam derivative, 2-methyl-2-acetoxymethyl-3-carbomethyl-6-phenoxyacetamidopenam. This material was rechromatographed for analysis.

Fractions 110–115, 15 mg., were primarily the cepham derivative, 3-methyl-3-acetoxy-4-carbomethoxy-7-phenoxyacetamidocepham.

Fractions 89–105, 130 mg., were a mixture comprising principally the penam and cepham products. This material, on being subjected to rechromatography, yielded 50 mg. of the cepham compound. Both this material and the material from fractions 110–115 were amorphous, and contained a small proportion of 3-methyl-4-carbomethoxy-7-phenoxyacetamide-Δ^3-cephem, as indicated by the nuclear magnetic resonance spectra.

The two products thus obtained were compared in antibiotic activity according to the following procedure. Samples of the products were individually incubated at pH 7 in phosphate buffer for 20 hours at 37° C. with shaking. At the end of the incubation period, the solutions were subjected to assay against various microorganisms by the conventional paper disc plate method. The incubated solutions were also tested by paper electrophoresis followed by bioautographic assay. Both the penam and the cepham were active against *Staphylococcus aureus* and *Bacillus subtilis*, but not against gram-negative organisms. The cepham produced a zone size approximately half as great as that produced by the penam at the same concentration. On paper electrophoresis of the two products, acid antibiotics were seen which had the same mobility as penicillin V.

Example 2

Δ^3-cephem derivative.—A solution of 5.0 g. of penicillin V sulfoxide methyl ester and 160 mg. of p-toluenesulfonic acid in 60 ml. of xylene was heated at reflux for one hour and was then evaporated to dryness at reduced pressure. The residue was dissolved in ethyl acetate and the resulting solution was washed successively with dilute aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution, then dried and evaporated at reduced pressure, yielding 4.5 g. of a dark-colored oil. The oil was chromatographed through 80 g. of silicic acid in a column with a mixture of chloroform and benzene (1:1) as the eluting solvent, the eluate being withdrawn in 7-ml. fractions. Fractions 115–225, 1.23 g., were combined and evaporated to dryness at reduced pressure, and the residue was crystallized from methanol-ether. The product weighed 306 mg. and melted at 137–138° C. A second crop of crystals weighed 174 mg. and melted at 128–136° C. Recrystallization yielded an analytical sample melting at 141–142° C.

Analysis.—Calc. for 3-methyl-4-carbomethoxy-7-phenoxyacetamido-Δ^3-cephem, $C_{17}H_{18}N_2O_5S$ (percent): C,

56.34; H, 5.00; N, 7.73; S, 8.85. Found (percent): C, 56.26; H, 5.08; N, 7.54; S, 8.93.

When subjected to incubation in pH 9 phosphate buffer for 20 hours at 37° C. with shaking, then subjected to assay by the paper disc plate method, the product showed antibacterial activity against *S. aureus* and *B. subtilis* which was not affected by penicillin β-lactamase.

Example 3

Δ³-cephem derivative, alternative preparation.—7-phenoxyacetamidocephalosporanic acid methyl ester (549 mg.) in dioxane (45 ml.) was contacted with hydrogen at room temperature and 1200 p.s.i. in the presence of 2.0 g. of 10 percent palladium-on-charcoal. The treated solution was filtered and evaporated to dryness at reduced pressure. The residue was subjected to chromatographic separation on 10 g. of silica gel (E. Merck), using 5 percent ethyl acetate in chloroform as the elution solvent.

Fractions 5 and 6, 97 mg., were a mixture of starting material and 3-methyl-4-carbomethoxy-7-phenoxyacetamido-Δ³-cephem. This material was rechromatographed using 2 percent ethyl ether in chloroform as the elution solvent, and 11 mg. of the Δ³-cephem compound were obtained which was identical in every way (infrared, ultraviolet, melting point, mixed melting point, X-ray diffraction) to that prepared by the sulfoxide rearrangement of Example 2.

Fractions 7–9, 275 mg., of the original chromatogram contained pure starting ester.

Fractions 10 et seq. yielded the dihydro derivative of the starting ester, as indicated by infrared, ultraviolet, and nuclear magnetic resonance spectra.

Example 4

Penicillin V sulfoxide benzhydryl ester.—Penicillin V sulfoxide in the form of 15.0 g. of the free acid was suspended in 200 ml. of ethyl acetate, and to the stirred suspension was added an excess of diphenyldiazomethane (Organic Syntheses, Collective Volume 3, page 351) in ether at room temperature. At the end of 20 minutes, a clear red solution had been obtained. The solution was allowed to stand overnight at room temperature and was then evaporated at reduced pressure. The residual material, a red gum, was crystallized from acetone and petroleum ether. The product, penicillin V sulfoxide benzhydryl ester, weighed 17.4 g. and melted at 155–156° C., $[\alpha]_D = +191.3°$.

Analysis.—Calc. for $C_{29}H_{28}N_2O_5S$ (percent): C, 65.39; H, 5.30; N, 5.26. Found (percent): C, 65.61; H, 5.29; N, 4.92.

Δ³-cephem benzhydryl ester.—Penicillin V sulfoxide benzhydryl ester (5.0 g.) and dry p-toluenesulfonic acid (140 mg.) were suspended in 100 ml. of xylene and refluxed for 30 minutes. The resulting solution was evaporated to dryness at reduced pressure. The residue was dissolved in ethyl acetate and washed successively with dilute aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution, and the washed solution was evaporated to dryness at reduced pressure, yielding 4.7 g. of crude product. Chromatography of this material through a silicic acid column with cyclohexane-methyl isobutyl ketone (4:1) as the eluting solvent yielded 422 mg. of the desired product, 3-methyl-4-carbobenzhydryloxy-7-phenoxyacetamido - Δ³ - cephem, melting at 156–157° C. after recrystallization from methanol and having $[\alpha]_D = +30.3°$.

Analysis.—Calc. for $C_{37}H_{34}N_2O_5S$ (percent): C, 67.68; H, 5.09; N, 5.44; S, 6.23. Found (percent): C, 67.63; H, 5.20; N, 5.26; S, 6.30.

Example 5

Acetoxycepham benzhydryl ester.—Penicillin V sulfoxide benzhydryl ester was reacted with acetic anhydride according to the procedure of Example 1. The product was a mixture of the benzhydryl esters of 2-methyl-2-acetoxymethyl - 6 - phenoxyacetamido-penam-3-carboxylic acid and 3-methyl-3-acetoxy-7-phenoxyacetamido-cepham-4-carboxylic acid.

Example 6

3 - methyl-7-phenoxyacetamido-Δ³-cephem-4-carboxylic acid.—3-methyl-4-carbobenzhydryloxy - 7 - phenoxyacetamido-Δ³-cephem (100 mg.) was dissolved in 6 ml. of dioxane containing a trace of dry hydrogen chloride, and to the solution was added a suspension of 200 mg. of prereduced 10 percent palladium-on-charcoal in dioxane. The mixture was agitated with hydrogen at room temperature and atmospheric pressure, and a hydrogen uptake of 3.98 ml. (theoretical, 4.75 ml.) was observed over a period of 18 hours. The hydrogenation product was filtered and evaporated to dryness at reduced pressure. The residue thus obtained was dissolved in ethyl acetate, layered with water, and adjusted to pH 7 with dilute aqueous sodium hydroxide solution. The layers were separated. The ethyl acetate phase was washed with water, dried, and evaporated to dryness at reduced pressure. The neutral material thus obtained, weighing 50 mg., was identical to the benzhydryl starting ester. The aqueous phase and washings were combined, layered with ethyl acetate, and acidified to pH 2 with dilute hydrochloric acid. The ethyl acetate phase was separated, washed with water, dried, and evaporated to dryness at reduced pressure. The acidic material thus obtained, weighing 16 mg., was the free acid, 3-methyl-7-phenoxyacetamido-Δ³-cephem-4-carboxylic acid, having a pK_a in 66 percent aqueous dimethylformamide of 5.7. The structure of the material was confirmed by its nuclear magnetic resonance spectrum. The potassium salt was prepared in crystalline form and was found to have an antibiotic assay against *Staphylococcus aureus* of 12 penicillin G units per milligram.

Example 7

The following additional compounds, illustrative of class Ib, above, were also prepared via hydrogenation of the 3-acetoxymethyl analogue as illustrated generally in Example 3, and all were found to be effective as antibiotics against penicillin-resistant strains of *Staphylococcus aureus*:

7-(D-α-aminophenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid

7-(dl-α-amino-m-chlorophenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid

7-(dl-α-amino-p-chlorophenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid

7-(dl-α-amino-p-chlorophenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid trifluoroacetate

7-(dl-α-amino-m-bromophenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid

7-(dl-α-amino-m-bromophenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid trifluoroacetate

7-(dl-α-amino-m-fluorophenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid

7-(dl-α-amino-m-methoxyphenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid

7-(dl-α-amino-m-methoxyphenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid trifluoroacetate

7-(D-α-amino-m-hydroxyphenylacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid

7-(p-chlorophenoxyacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid potassium salt

7-(m-nitrophenoxyacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid potassium salt

7-phenylmercaptoacetamido-3-methyl-Δ³-cephem-4-carboxylic acid potassium salt

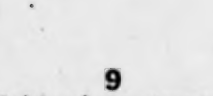
7-(n-butylmercaptoacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid potassium salt

7-(m-chlorophenylmercaptoacetamido)-3-methyl-Δ³-cephem-4-carboxylic acid potassium salt

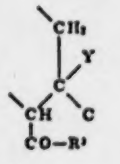
7-(o-trifluoromethylphenylmercaptoacetamido)-3-methyl-Δ^3-cephem-4-carboxylic acid potassium salt

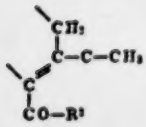
We claim:

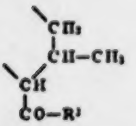
1. A compound of the structure



where R^1 is a member of the group represented by the following formulas:







Y is C_2–C_4 alkanoyloxy or C_1–C_4 alkoxy;

R^2, when connected directly to the molecule, is $-NH_2$, —NH—(C_1–C_4 alkyl), or —N=di(C_1–C_4 alkyl); and

R_3, when connected through —O— to the molecule, is hydrogen, a pharmaceutically acceptable cation, C_1–C_4 alkyl, C_4–C_7 cycloalkyl, or phenyl;

R is a member of the group represented by the following formulas:

R^3—O—CH_2—

and

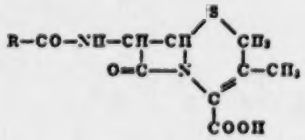
R^3—S—CH_2—

R_3 is phenyl or phen(C_1–C_4)alkyl;

R^4 is hydrogen or methyl; and

R^3 is C_1–C_3 alkyl, phenyl or phen(C_1–C_4)alkyl.

2. A compound as in claim 1, having the structure



where R is a member of the group represented by the following formulas:

R^3 is phenyl or phen(C_1–C_4)alkyl;

R^4 is hydrogen or methyl; and

R^3 is C_1–C_4 alkyl, phenyl or phen(C_1–C_4)alkyl.

3. A compound as in claim 1, said compound being 3 - methyl - 3 - acetoxy - 4 - carbomethoxy - 7 - phenoxyacetamidocepham.

4. A compound as in claim 1, said compound being 3-methyl-4-carbomethoxy-7-phenoxyacetamide-Δ^3-cephem.

5. A compound as in claim 1, said compound being 3-methyl - 4 - carbobenzhydryloxy-7-phenoxyacetamido-Δ^3-cephem.

6. A compound as in claim 1, said compound being 3 - methyl - 3 - acetoxy - 7 - phenoxyacetamidocepham-4-carboxylic acid.

7. A compound as in claim 1, said compound being 7-phenoxyacetamide-3 - methyl-Δ^3-cephem-4 - carboxylic acid.

8. A compound as in claim 1, said compound being 7 - phenylmercaptoacetamido - 3 - methyl - Δ^3 - cephem-4-carboxylic acid.

9. A compound as in claim 1, said compound being 7 - (n - butylmercaptoacetamido) - 3-methyl-Δ^3-cephem-4-carboxylic acid.

10. A compound as in claim 1, said compound being 7-(m-chlorophenylmercaptoacetamido) - 3 - methyl-Δ^3-cephem-4-carboxylic acid.

11. A compound as in claim 1, said compound being 7 - (o - trifluorometnylphenylmercaptoacetamido) - 3-methyl-Δ^3-cephem-4-carboxylic acid.

12. A compound as in claim 1, said compound being 7-(α-aminophenylacetamido)-3-methyl-Δ^3 - cephem - 4-carboxylic acid.

13. A compound as in claim 1, said compound being 7-(α-amino-m-chlorophenylacetamido) - 3 - methyl-Δ^3-cephem-4-carboxylic acid.

14. A compound as in claim 1, said compound being 7-(p-chlorophenoxyacetamido) - 3 - methyl - Δ^3-cephem-4-carboxylic acid.

15. A compound as in claim 1, said compound being 7-(α-amino-m - hydroxyphenylacetamido) - 3 - methyl-Δ^3-cephem-4-carboxylic acid.

16. 7-(D-α-aminophenylacetamido) - 3 - methyl - Δ^3-cephem-4-carboxylic acid.

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